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PHOTOCHEMICAL SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A THESIS SUBMITTED BY LAURENCE R.B. BRYANT

A CANDIDATE FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

OF THE

OPEN UNIVERSITY

DECEMBER 1982

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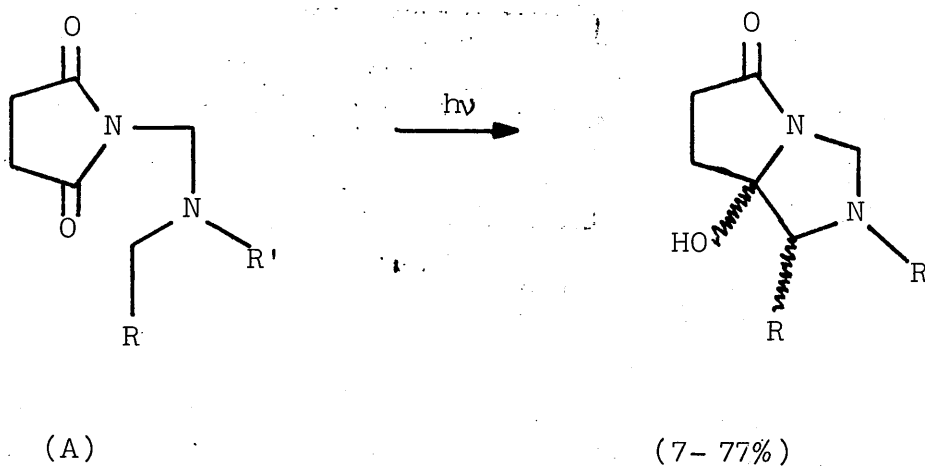
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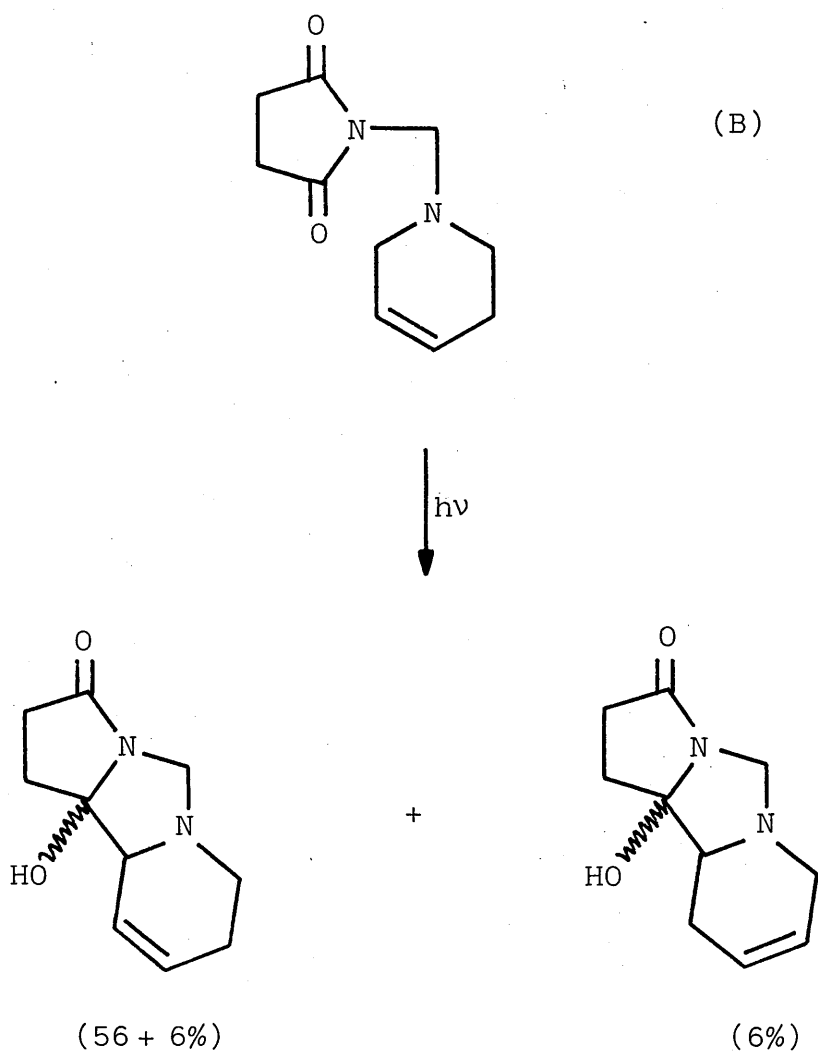
ABSTRACT

The aim of our research was to investigate the photocyclisation of N-substituted imide systems, in order to prepare polycyclic heterocyclic photoproducts of potential pharmaceutical interest.

The major group of substrates were N-(dialkylamino-alkyl)succinimides. Irradiation of succinimide Mannich bases (A) leads to two diastereoisomers of 1,3-diazabicyclo[3.3.0]octanes in reasonable yields. The relative stereochemistry was assigned on the basis of spectral data.

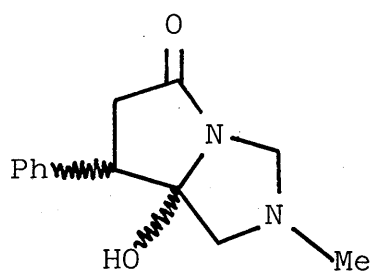
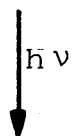
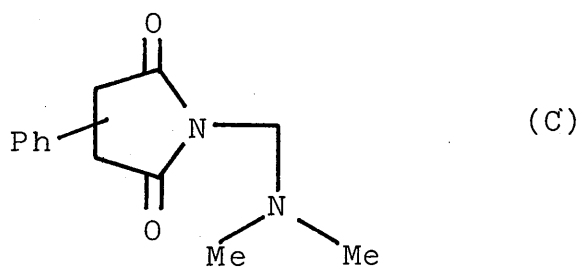


With substrates (e.g. B) derived from unsymmetrical amines, there is strong orientational preference.

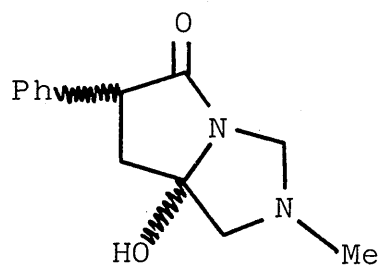


Substrates (e.g. C) derived from an unsymmetrical succinimide gave a mixture of products; the preferred orientation of cyclisation is to the more hindered C-1 carbonyl group.

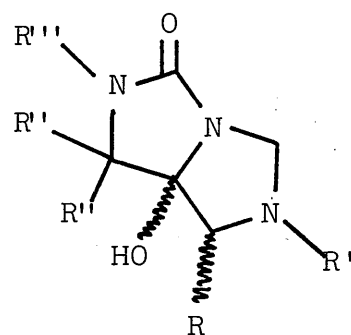
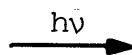
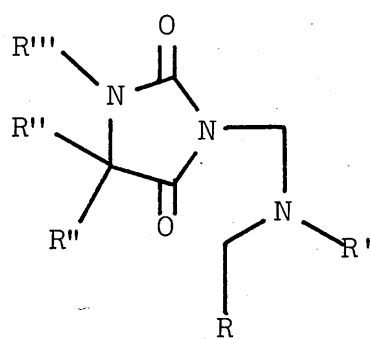
Using hydantoin substrates (D) which correspond to succinimides in which a methylene group is replaced by a heteroatom, we found that cyclisation occurs only at the C-4 (imide-like) carbonyl group to give diastereoisomers of 1,3,7-triazabicyclo[3.3.0]octanes.



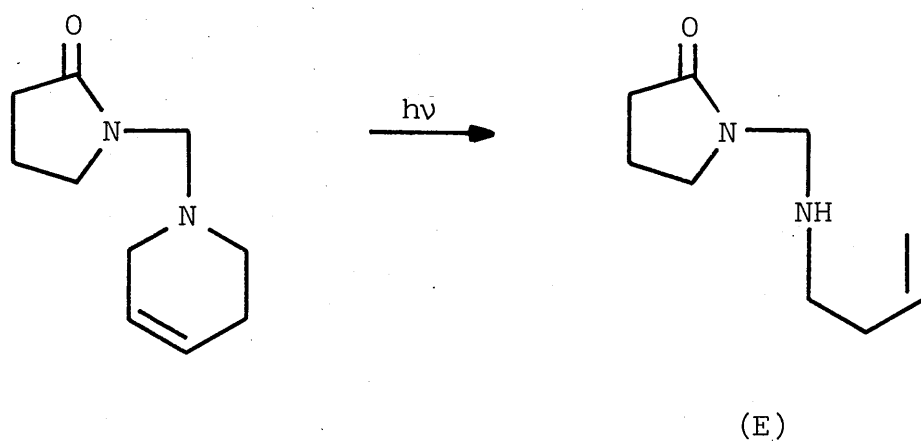
(34 + 15%)



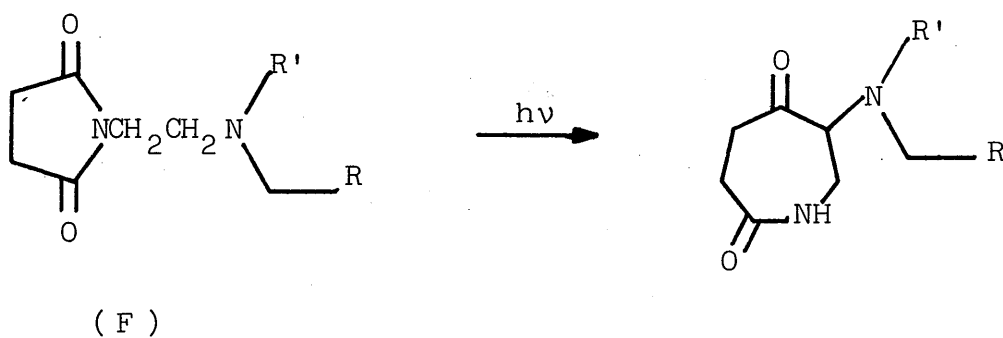
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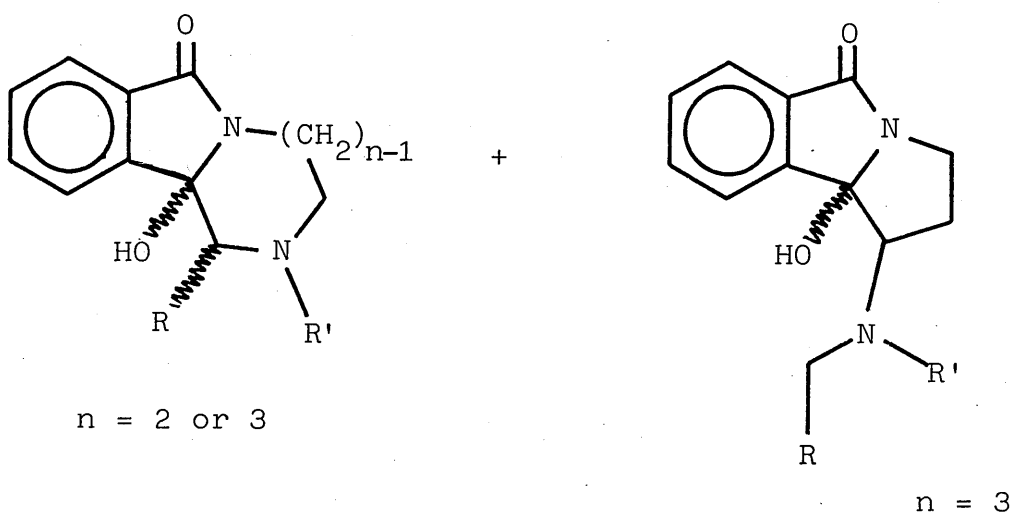
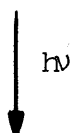
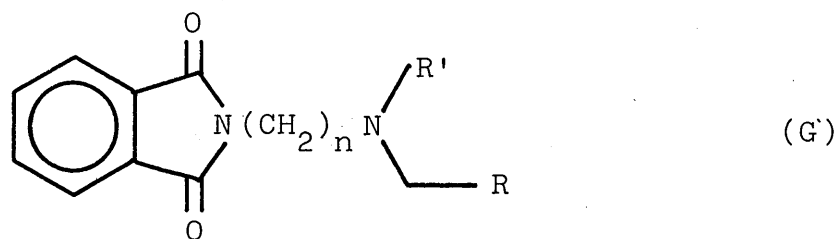


Glutarimide Mannich bases show many parallels with the succinimide analogues. However, pyrrolidin-2-one Mannich bases did not afford photocyclised products. A minor product (E) is formed by cleavage in the amine fragment.



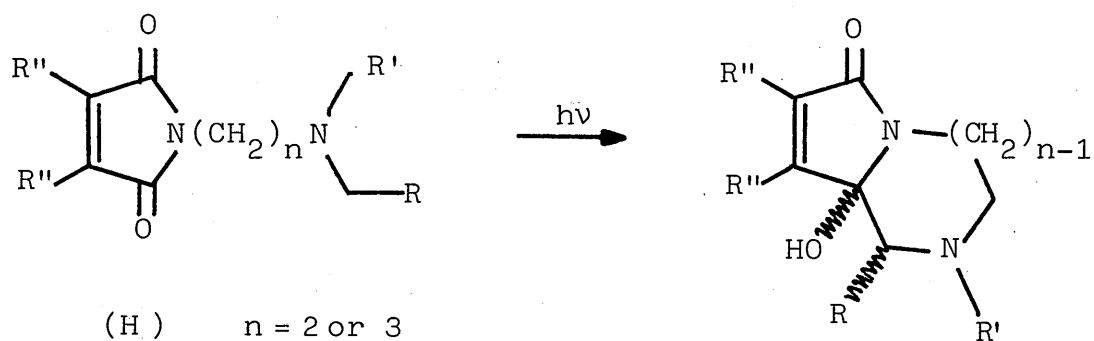
N-(Dialkylaminoethyl) derivatives of saturated imides (F) give rise to ring-expanded photoproducts. This is in contrast to phthalimide substrates (G; $n = 2$), where photoproducts with a new piperazine ring are obtained.





Our hypothesis is that an electron-transfer mechanism operates in the aromatic systems, leading to the possibility of medium/large ring formation, but this is not effective in the succinimides which are poorer electron acceptors. To test this, we irradiated a series of N-(dialkylaminoalkyl) derivatives of imides with a double bond conjugated with the carbonyl groups, and found that these substrates (H) do give photoproducts with new six- or seven-membered

rings.



Our results with N-(dialkylaminopropyl)phthalimides (G; n = 3) are not entirely in agreement with earlier reports that medium-ring formation is the major photocyclisation process for phthalimide substrates. Further work is required to extend this comparison of the photocyclisation process for saturated, unsaturated and aromatic N-(dialkylaminoalkyl)imides.

ACKNOWLEDGEMENTS

I wish to express my gratitude to my Supervisor, Dr. J.D. Coyle for the expert guidance he has given me over the past three years; to the team at Reckitt and Colman Pharmaceutical Division (Hull), especially Dr. M.R. Stillings for his helpful discussions on the process and handling of liquid products around Hull. My thanks also to all the research staff of the Chemistry Department of the Open University for some invaluable help and ideas, and to SERC who awarded me the CASE student-ship.

I would also like to thank my parents for their support over the past years and my wife, Susie, who has had to put up with me, and, of course, without her (and the typewriter) this manuscript would not have been possible.

C O N T E N T S

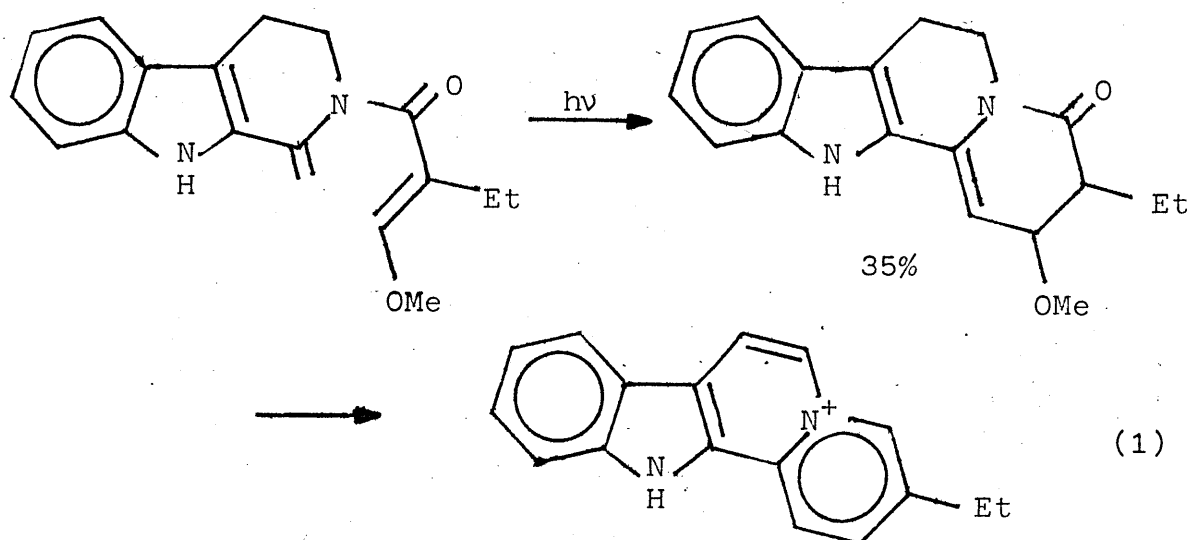
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CHAPTER ONE

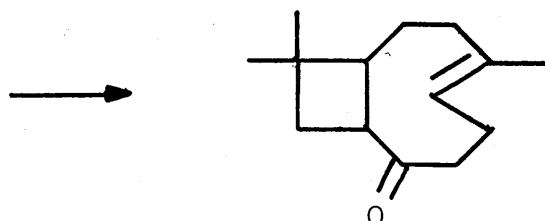
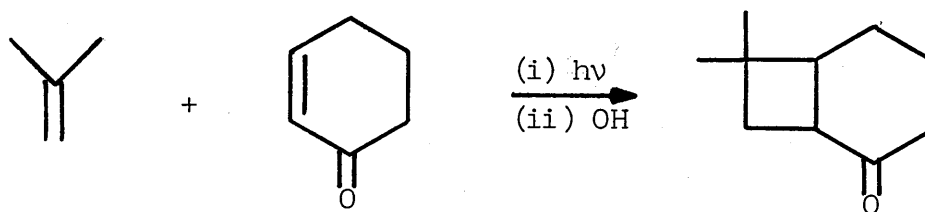
INTRODUCTION

Over the past 25 years, photochemical reactions have been increasingly used by chemists as valuable stages in organic syntheses. Their value lies mainly in the fact that photochemical excitation of a molecule changes the electron distribution and so makes possible reactions that are not typical of the ground state.¹

Photochemical cyclisation for instance is widely applicable in the synthesis of many alkaloids.² As an example, the strychnos alkaloid, flavopereirine has been prepared using the photocyclisation of an enamide of harmalane (1).³



Cyclobutane derivatives are potentially useful in natural product synthesis, and they can often be made by the irradiation of α,β -unsaturated ketones in the presence of alkenes. Cyclohexenone and 2-methylpropene on irradiation give a cyclobutane which can be further transformed to caryophyllene (2).⁴

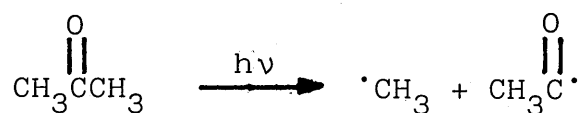


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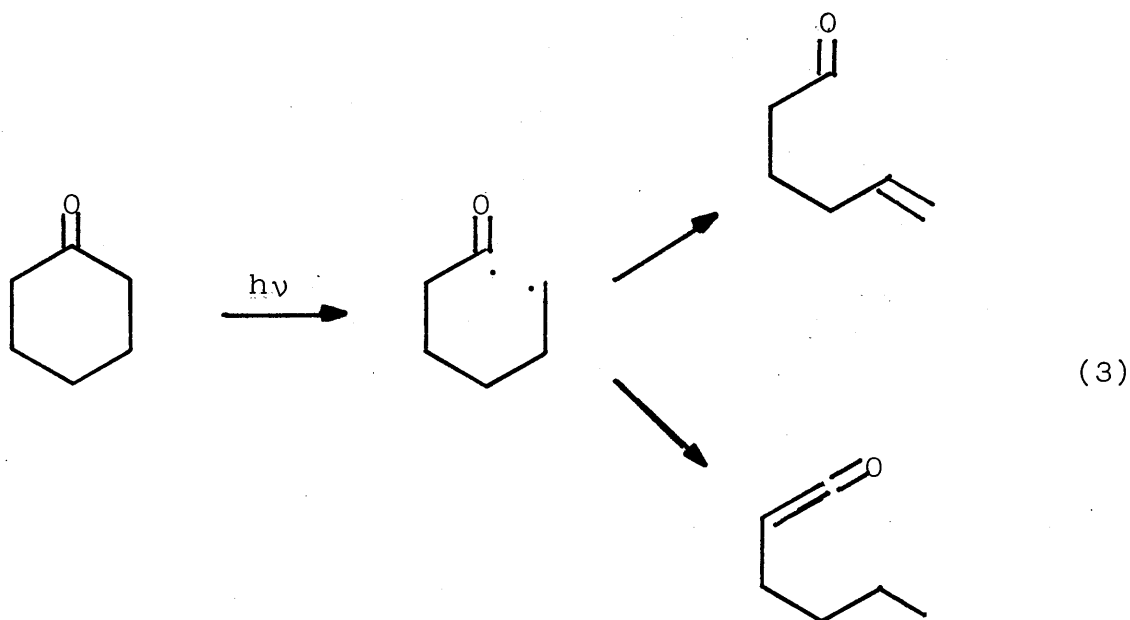
Our interest lies in the application of photochemical processes to the synthesis of heterocyclic compounds and specifically photoreactions of certain nitrogen-containing carbonyl compounds. Compounds containing the carbonyl chromophore are the most widely and intensively investigated in photochemistry.^{5,6} The main reaction types for the excited states of saturated (or certain aromatic) ketones with lowest (n, π^*) excited states are α -cleavage, addition to multiple bonds and hydrogen abstraction.

(a) α -Cleavage

This involves breaking of a bond adjacent to the carbonyl group to give two radical fragments (Norrish type 1 process). The initial process for acetone is:

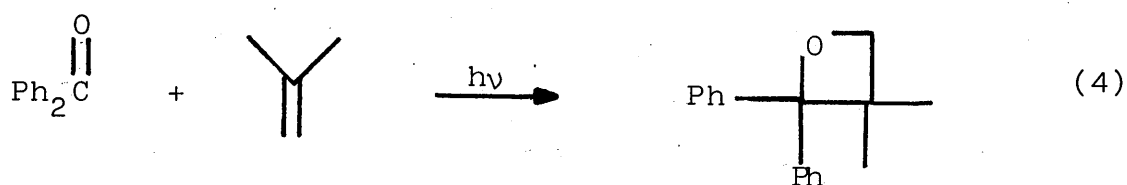


In cyclic systems, intramolecular secondary processes can take place which are not possible in the acyclic systems. α -Cleavage produces a biradical which can undergo one of two hydrogen-transfer processes in which a hydrogen atom is transferred to one radical centre from the atom adjacent to the other radical centre. The products from a cyclic ketone are an unsaturated aldehyde or a ketene (3).⁷

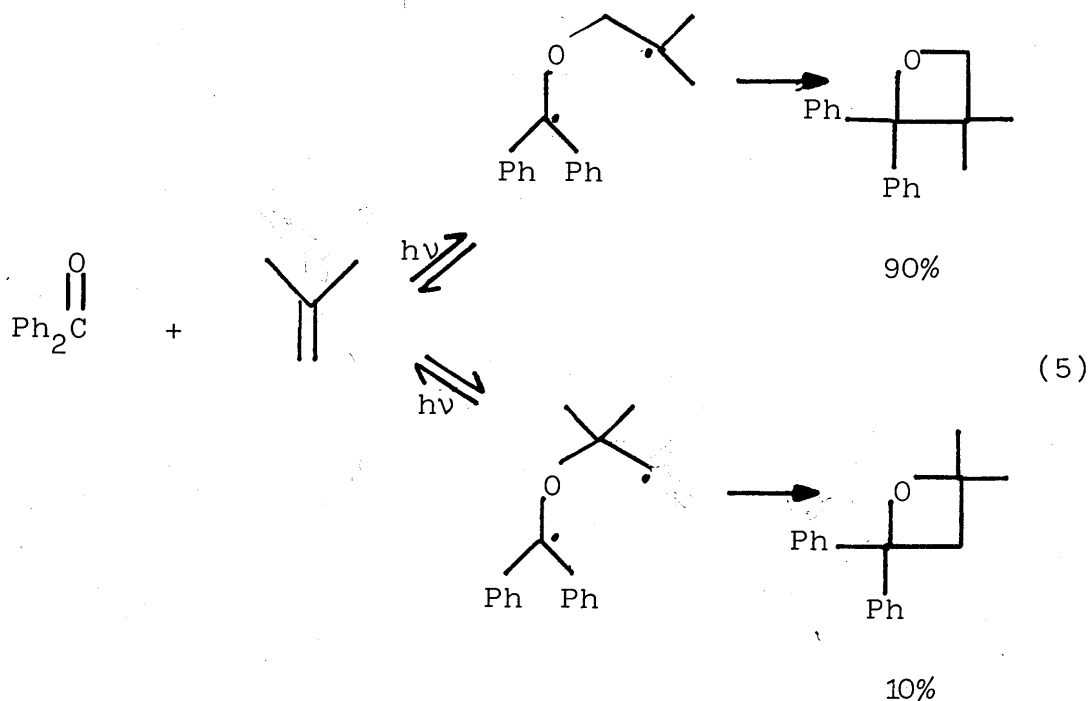


(b) Addition to multiple bonds

Photolysis of carbonyl compounds in the presence of alkenes give 4-membered oxygen heterocycles, oxetanes,⁸ by an overall cycloaddition reaction (4).

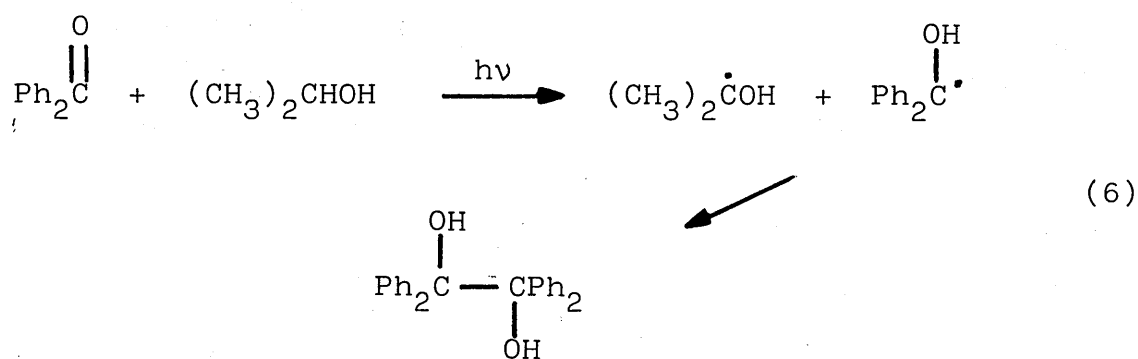


The reaction of an aromatic ketone involves attack on the ground state alkene by the (n,π^*) excited state of the carbonyl compound, i.e. addition to an alkene through an electron-deficient oxygen. The reactions are not stereospecific, although there is a preference for one orientation of addition (5). The more stable of the two possible biradicals is formed more readily, and assuming that the proportion of biradicals which undergo ring closure to give oxetane, rather than cleavage to give starting materials, is similar for both biradicals, the preferential formation of one oxetane is accounted for.

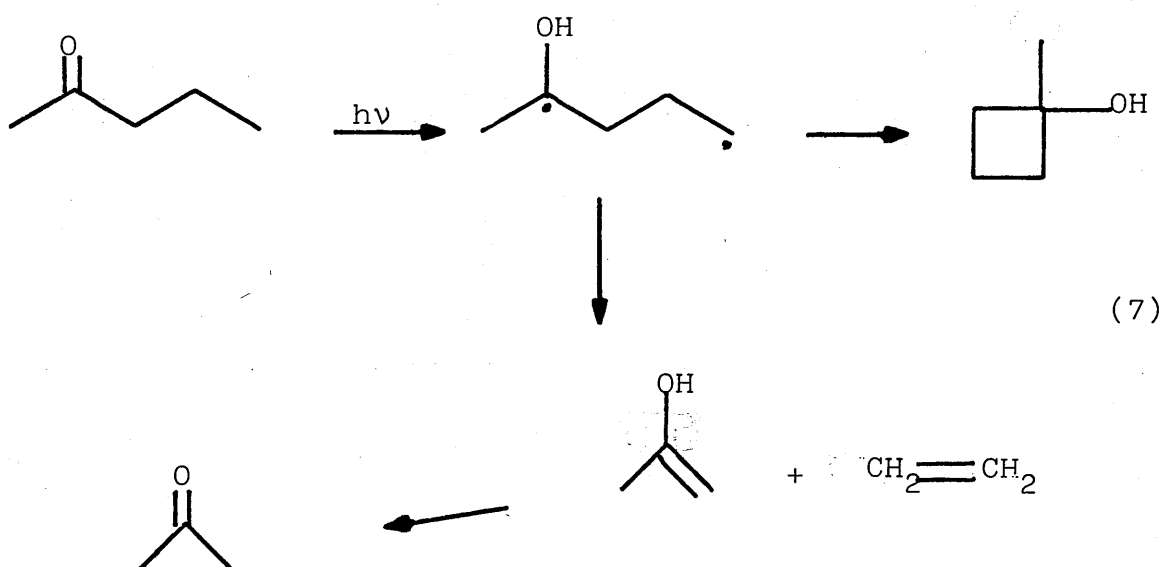


(c) Hydrogen abstraction

This involves transfer of a hydrogen atom to the oxygen atom of an excited state carbonyl chromophore from a donor molecule which may be solvent or added reagent. This process can give rise to overall reduction products (6).

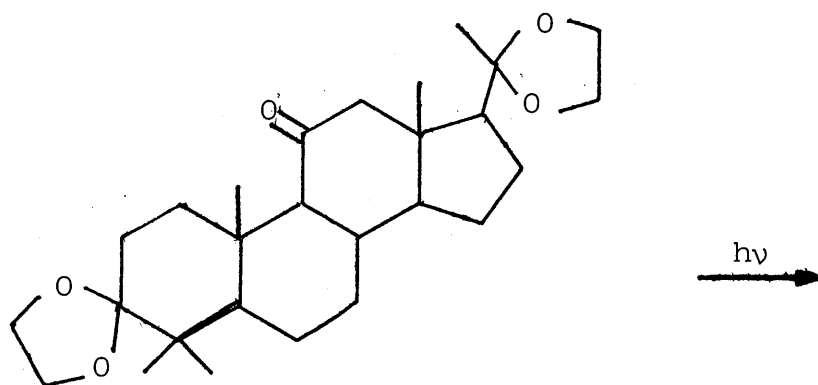


If the carbonyl compound has an accessible hydrogen atom in the γ -position within the molecule, products are formed that can be explained in terms of intramolecular hydrogen abstraction by the excited carbonyl group. The products arise from an initially formed biradical which can undergo bond cleavage to give a shorter chain carbonyl compound and an alkene by an overall elimination mechanism (Norrish type 2 process), or radical combination to produce a cyclobutanol by an overall cyclisation mechanism (7).

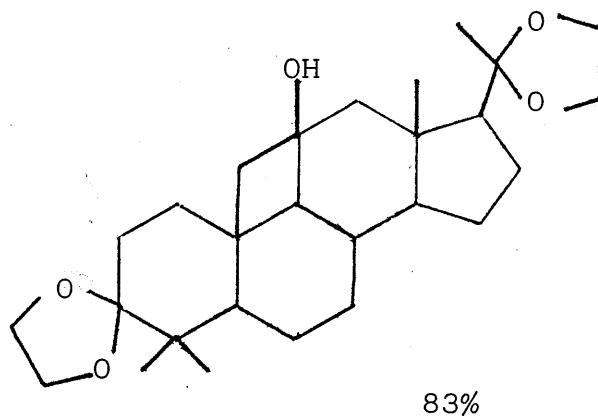


The enol form of the shorter chain carbonyl product has been observed by IR,¹⁰ and also by NMR.¹¹

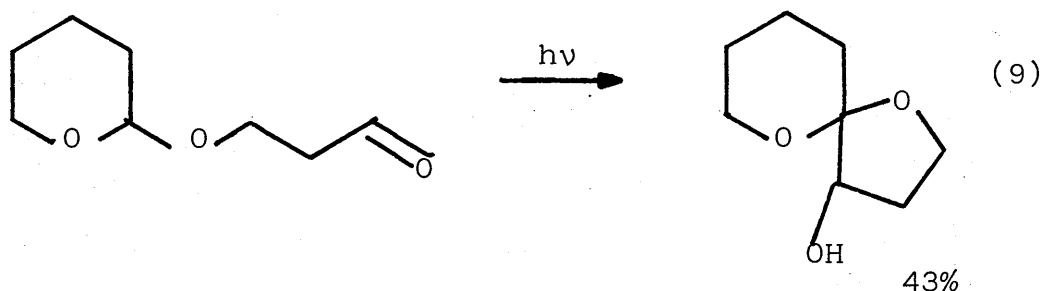
Cyclisation is often the minor reaction pathway, but the proportion of cleavage to cyclisation varies with structure, and the rigidity of the molecule can have a major influence. For certain systems, where the molecule is rigid, cyclisation is very efficient, as is the case for a number of steroids(8).¹²



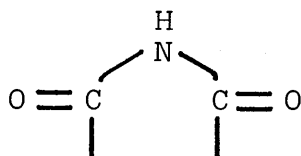
(8)



Systems without a hydrogen atom in the γ -position often give products by abstraction from another position. Photolysis of a (tetrahydropyranyloxy)propanal gives a cyclised product by δ -hydrogen abstraction (9).¹³



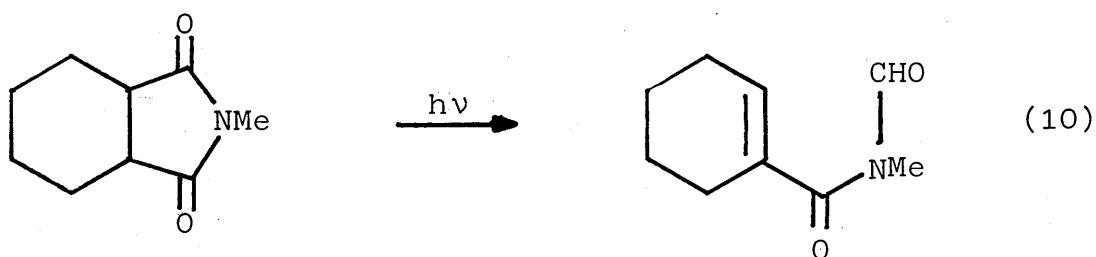
The carbonyl compounds whose photochemistry is of particular interest in our work are not ketones but those containing the imide moiety:



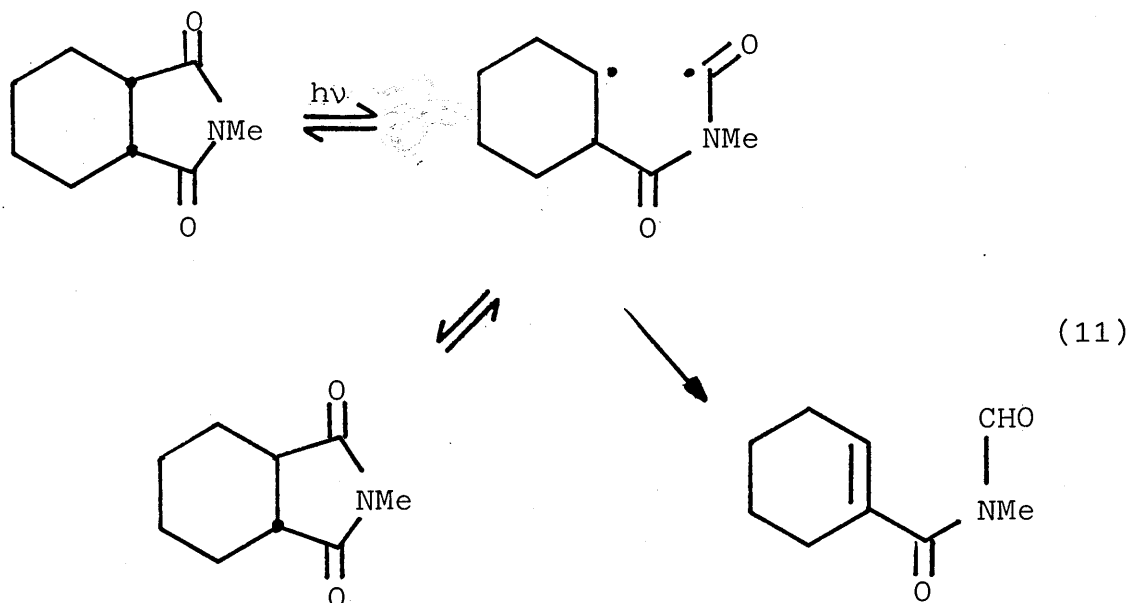
Simple amides often undergo inefficient photoreactions that are not synthetically useful,¹⁴ but imides undergo most of the known photoreactions of other carbonyl systems and some unprecedented reactions.^{15,16} The majority of work on these systems has been centred around cyclic imides and their nitrogen substituted derivatives.

α -Cleavage

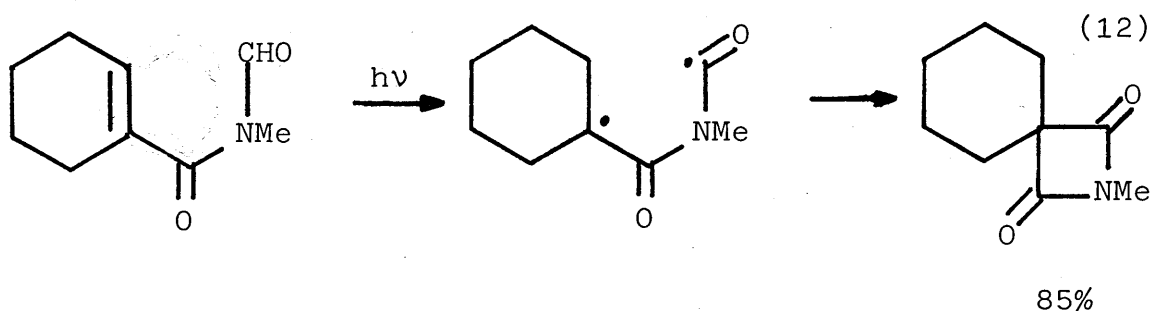
For aliphaticimides, there are a number of interesting photoreactions that involve α -cleavage in the imide excited state. From a synthetic point of view the most important reactions are the generation of ring-opened unsaturated amides by the photolysis of succinimides e.g. (10).¹⁷⁻¹⁹



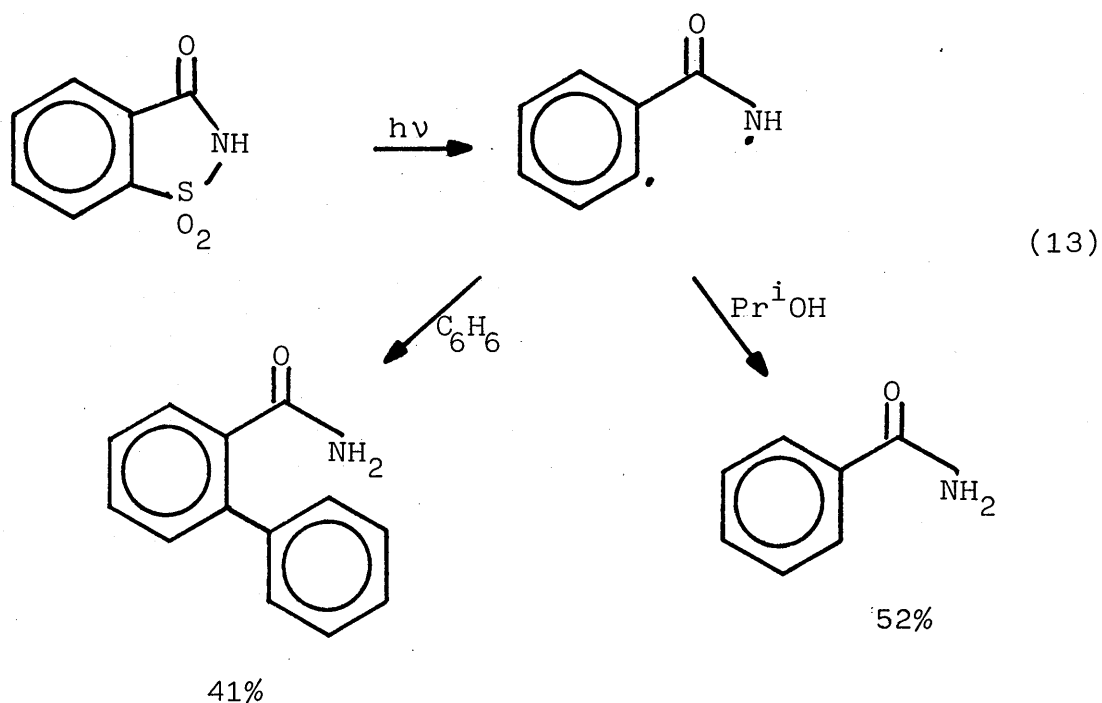
The mechanism is thought to involve initial α -cleavage to a biradical, followed by intramolecular hydrogen transfer to give the unsaturated formimide (11).



The reversal of biradical formation can lead to stereo-isomerisation of the starting materials. Further photochemical reaction of the unsaturated formimide leads to the formation of azetidine-2,4-diones by a process involving initial hydrogen transfer to the C=C double bond from the excited formyl group (12).

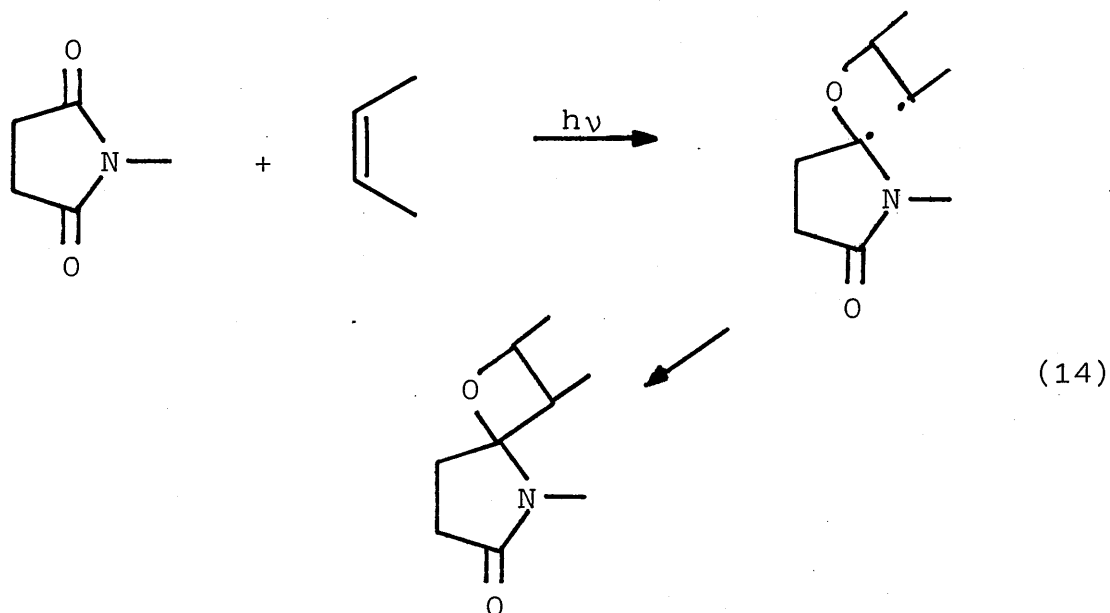


Phthalimides cannot undergo this type of reaction, and the only example of a compound related to phthalimide that takes part in an α -cleavage process is saccharin,²⁰ which loses sulphur dioxide on irradiation to give products derived from the resulting biradical (13).

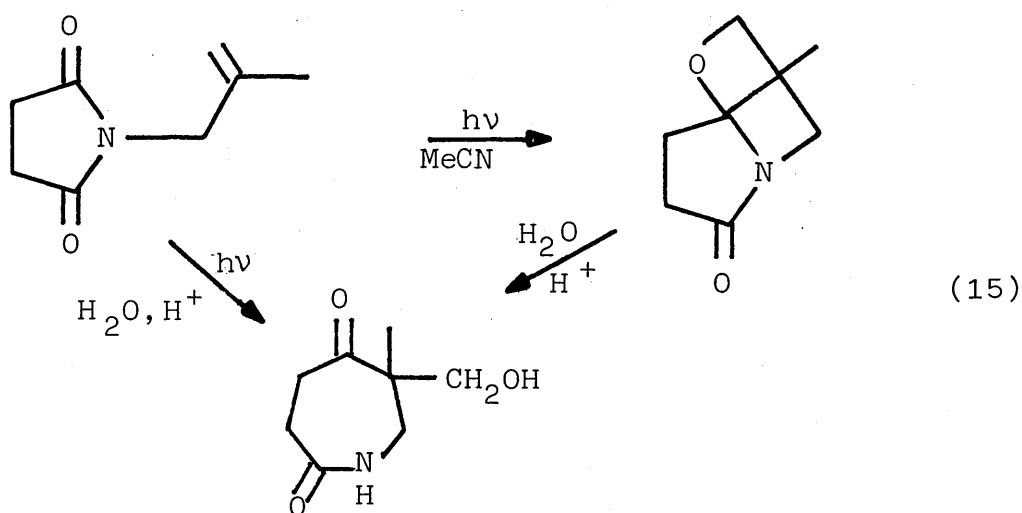


Addition to multiple bonds

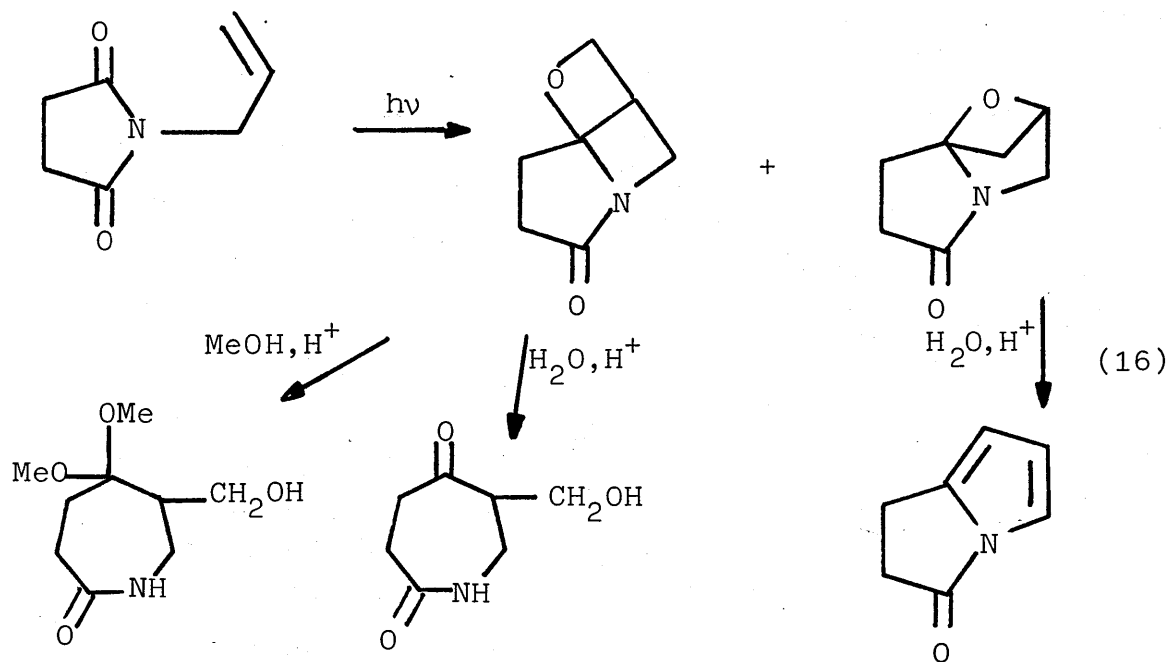
On irradiation of ketones or aldehydes with alkenes, oxetanes are formed by cycloaddition, and a similar process occurs with alicyclic imides such as succinimides or glutarimides (14).^{21,22}



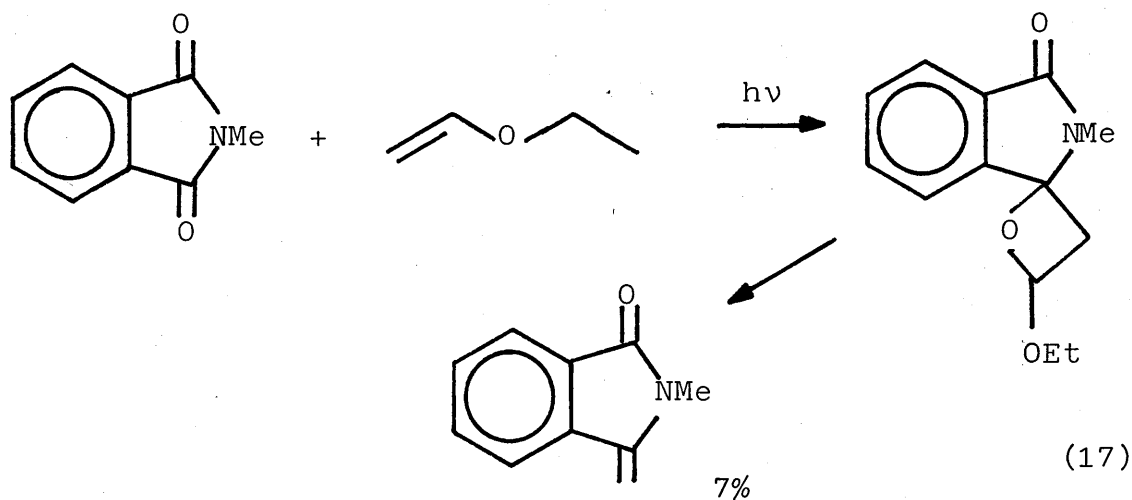
These reactions can also occur within the molecule to give tricyclic products, but usually these oxetanes are not isolated, and in many cases the product from an N-alkenylsuccinimide is an azepinedione (15).



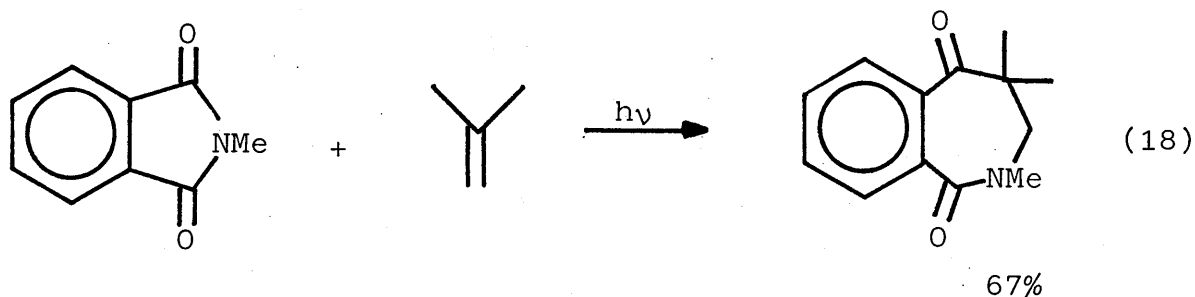
Other products which can be rationalised as arising from oxetanes have been prepared by irradiating in acidic alcoholic solvents (16).



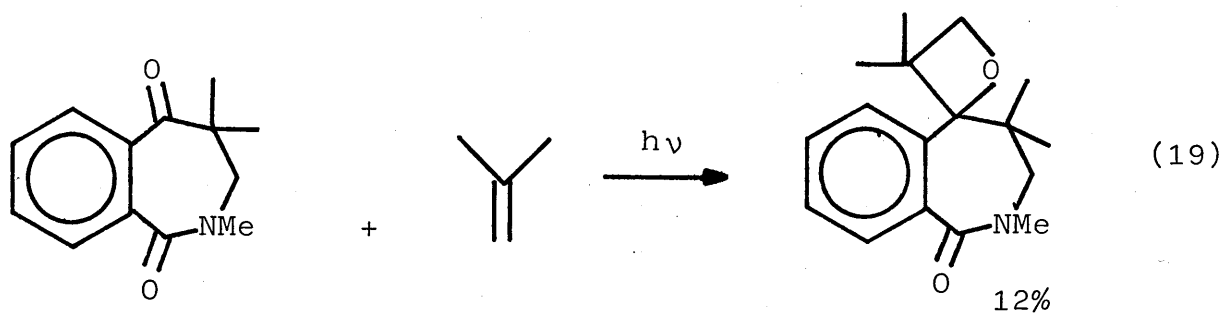
Phthalimides behave differently in their reaction with alkenes, and only in the case of N-methylphthalimide with ethyl vinyl ether²³ is a product isolated that is suggested to be derived by the decomposition of an initially formed oxetane (17).



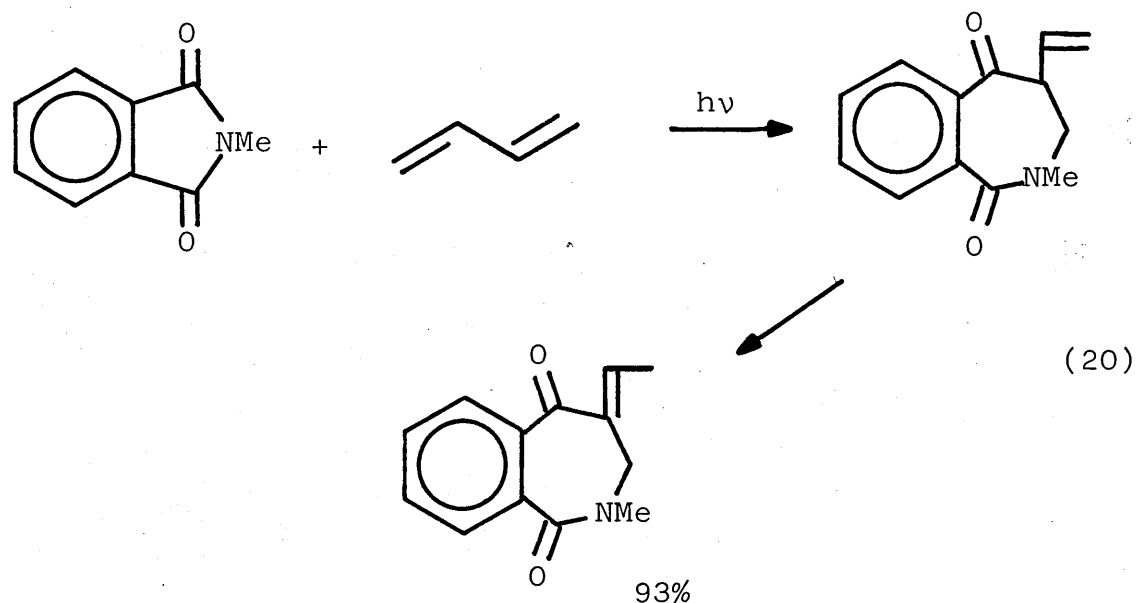
More typically, photolysis of phthalimides with alkenes gives benzazepinediones by ring expansion (18).^{21,24}



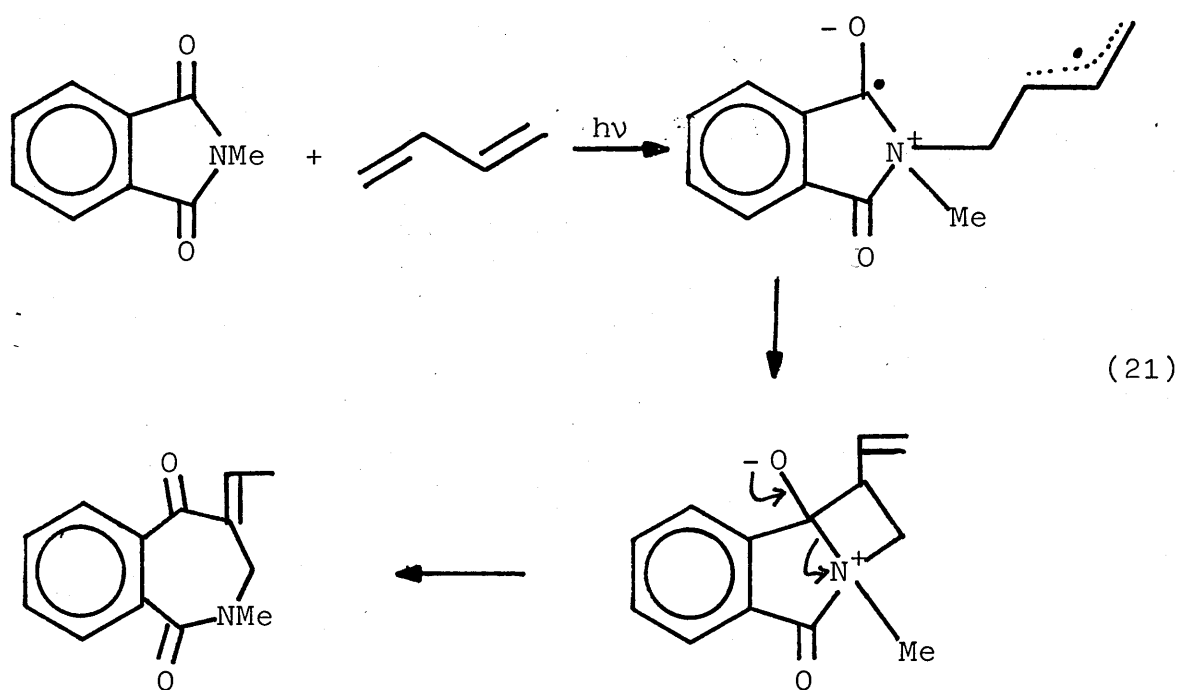
The product can undergo further photochemical reaction with more alkene to give a spiro-oxetane,²⁴ where the carbonyl group is behaving as in normal aromatic ketones (19).



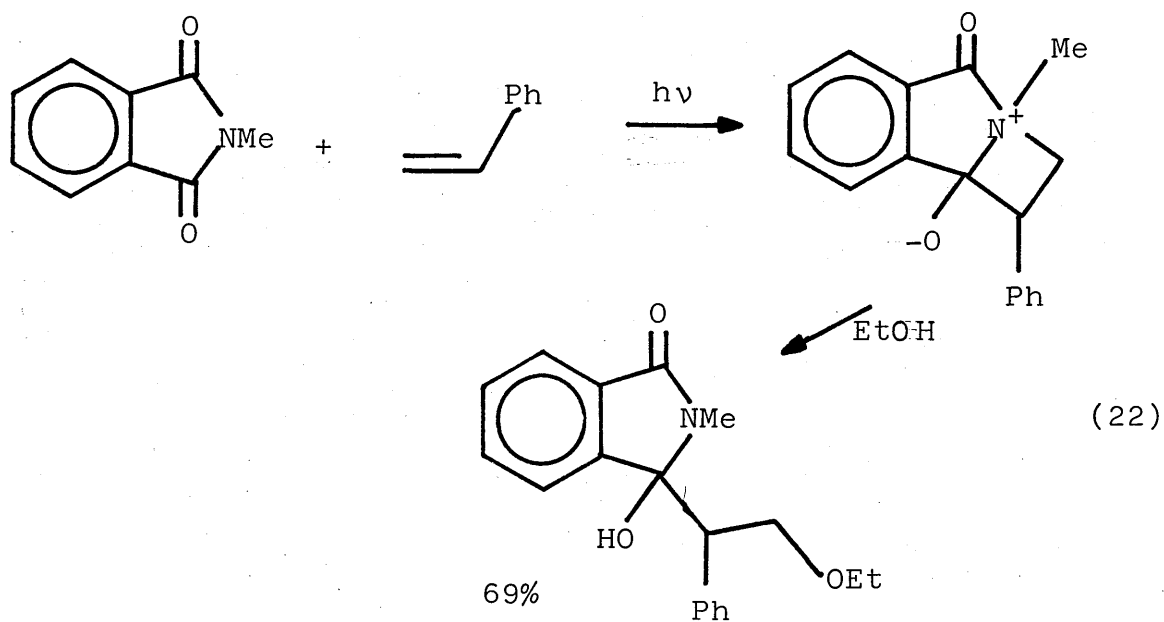
The first reported example of this photoaddition process was the reaction between N-methylphthalimide and butadiene (20).²⁵



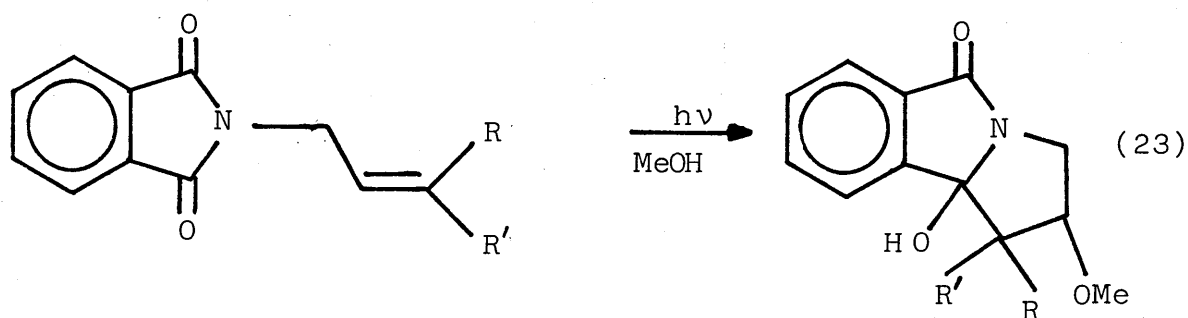
The product, isolated in very high yield, has undergone a shift of the double bond compared with the structure expected on the basis of the alkene photoproducts. The mechanism proposed for the ring-expansion involves zwitterionic intermediates (21).



Irradiation of phthalimides with alkenes in hydroxylic solvents gives rise to photoaddition products with solvent incorporation. The formation of these products supports the intermediacy of charged species in the mechanism for the photoaddition process (22).^{26,27}

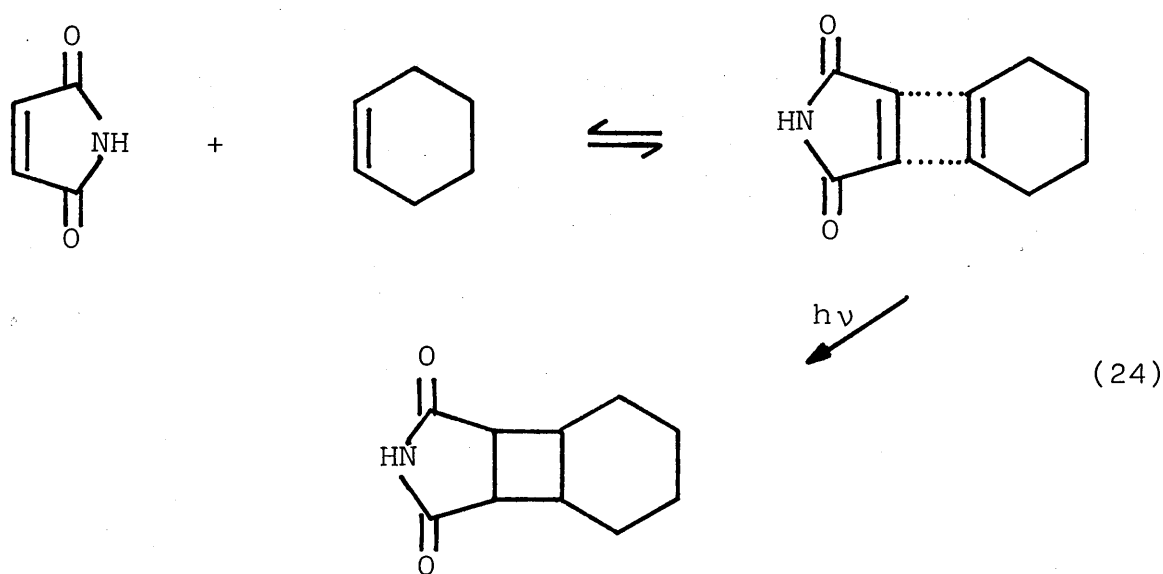


Intramolecular addition of an alkene with solvent incorporation takes place on irradiating N-allylic phthalimides in methanol (23).^{28,29}

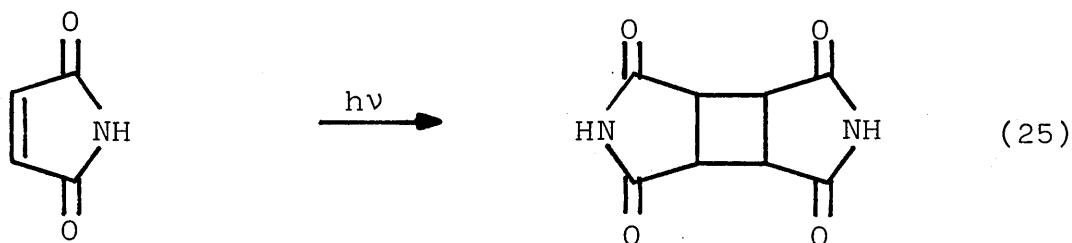


69-85% ($R, R' = H, Me, Ph$)

An alicyclic imide system whose photoaddition reactions has been investigated for different reasons is maleimide.³⁰ However, the observed reactions have involved the C=C double bond of the imide; this kind of process dominates maleimide photochemistry rather than reaction at the C=O double bond of the imide. As an example, intramolecular photocycloaddition of maleimide (or maleic anhydride) to cyclohexene gives a cyclobutane (24).



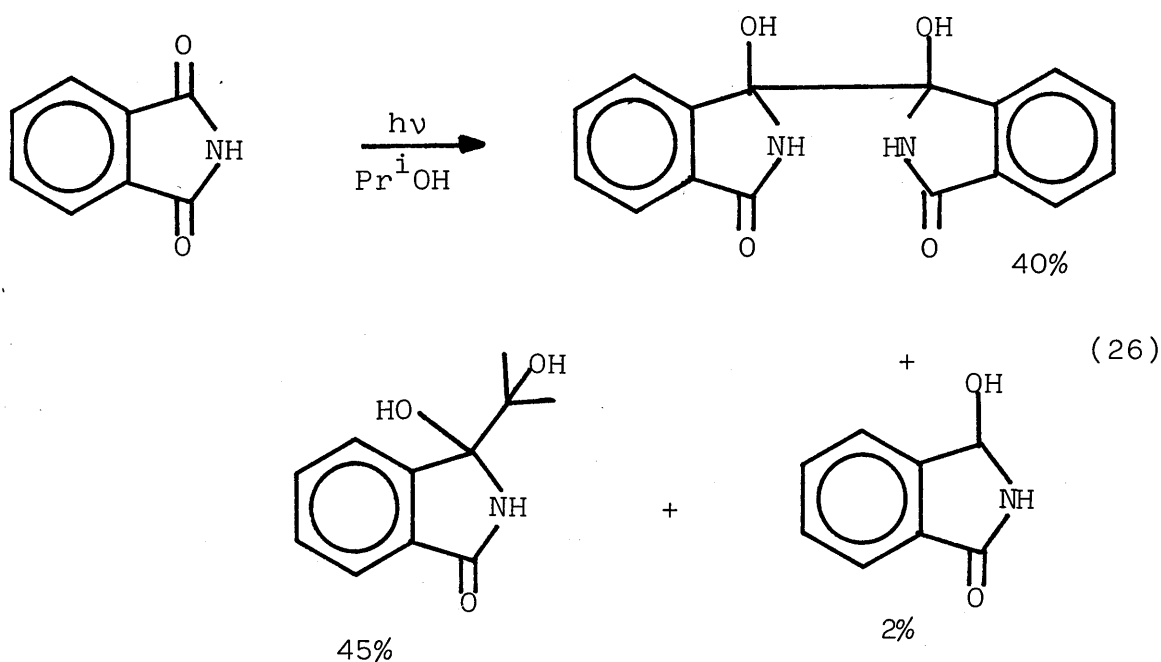
The reaction is thought to occur via a ground state charge-transfer complex, which absorbs light at longer wavelengths than either the alkene or maleic acid derivative.³¹ Irradiation of maleimide itself produces cyclobutanes, as maleimide dimers (25).³⁰



Hydrogen abstraction

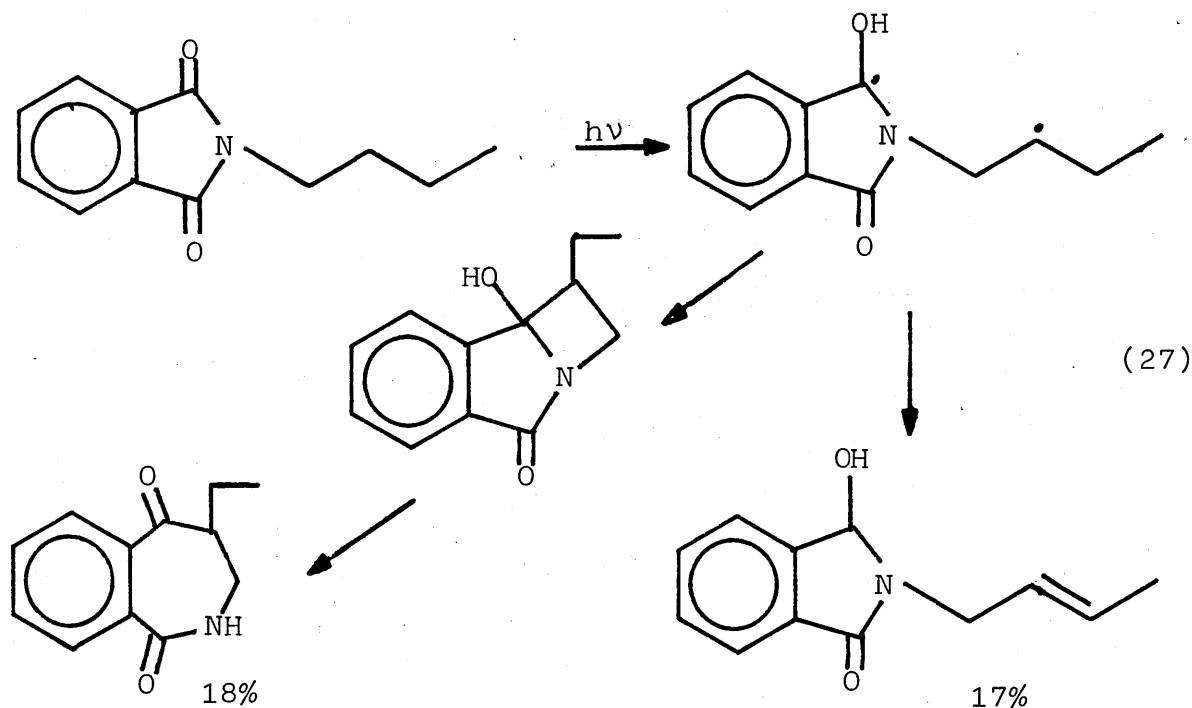
(i) Aromatic imides

In their ability to abstract hydrogen from a suitable donor such as an alcohol, ether, alkene or amine, phthalimides resemble aromatic ketones, giving photoreduction and photoaddition products. From the photolysis of phthalimides with most hydrogen donors, the major products are: a pinacol-like photoreduction product, a photoadduct and a more fully reduced 3-hydroxy-isoindolinone (26).³²



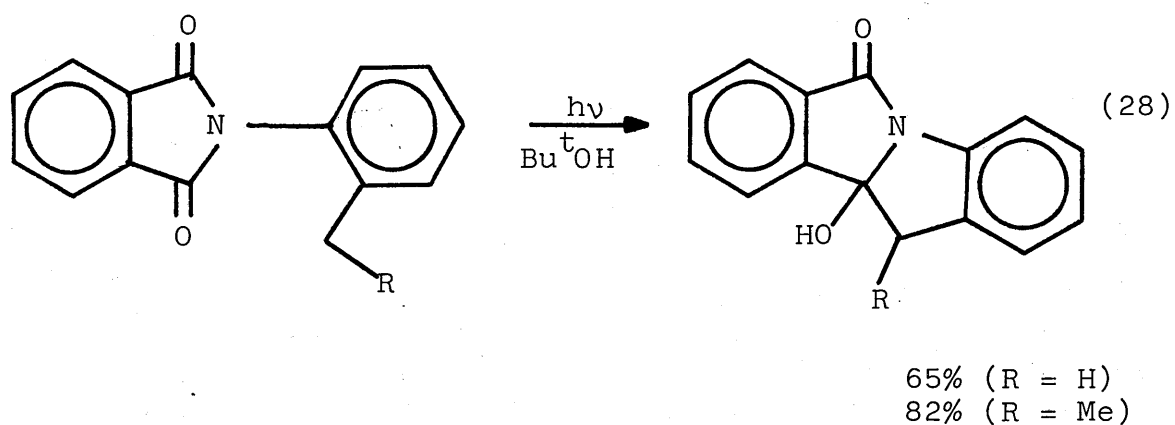
Hydrogen abstraction can also take place internally, resulting in cyclisation products. Intramolecular photochemical hydrogen abstraction has been the subject of many reports,^{33,34} the main reason being the possibility of preparing a variety of polycyclic heterocyclic systems. Photolysis of N-alkylphthalimides can give benzazepinediones, that arise by way of γ -hydrogen

transfer and an intermediate fused azetidinol.³⁵ Intramolecular disproportionation in the biradical intermediate sometimes occurs to give an N-allylic 3-hydroxy-isoindolinone (27).

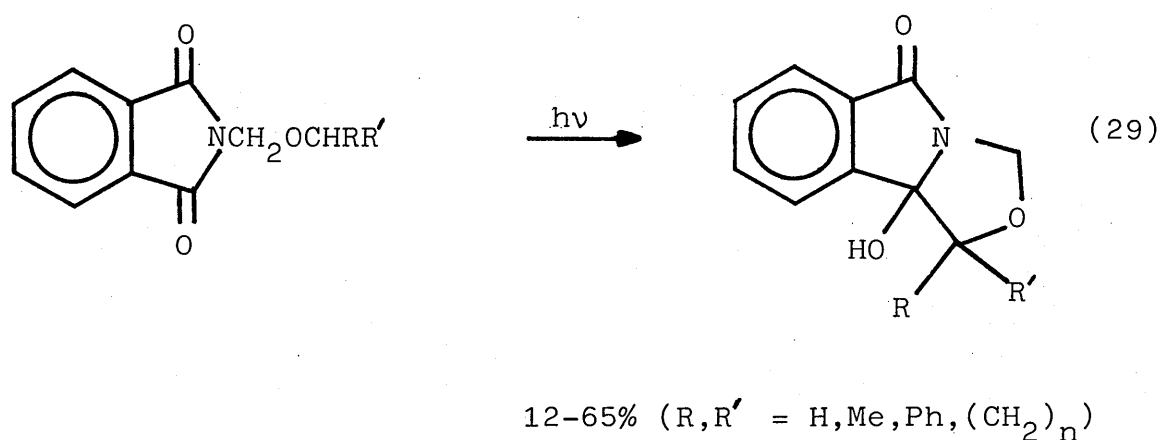


It is significant that this reaction and others of a similar type do not produce much phthalimide as a photoproduct, indicating that N-alkylphthalimides do not undergo intramolecular photoelimination reactions (Norrish type 2) as do aromatic ketones. This suggests that the orbitals containing the unpaired electrons and the bond being broken are not parallel, as is required for efficient cleavage of the biradical.³⁶

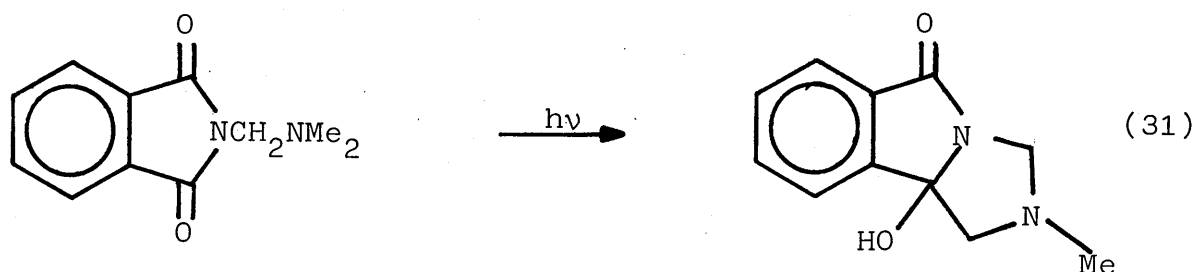
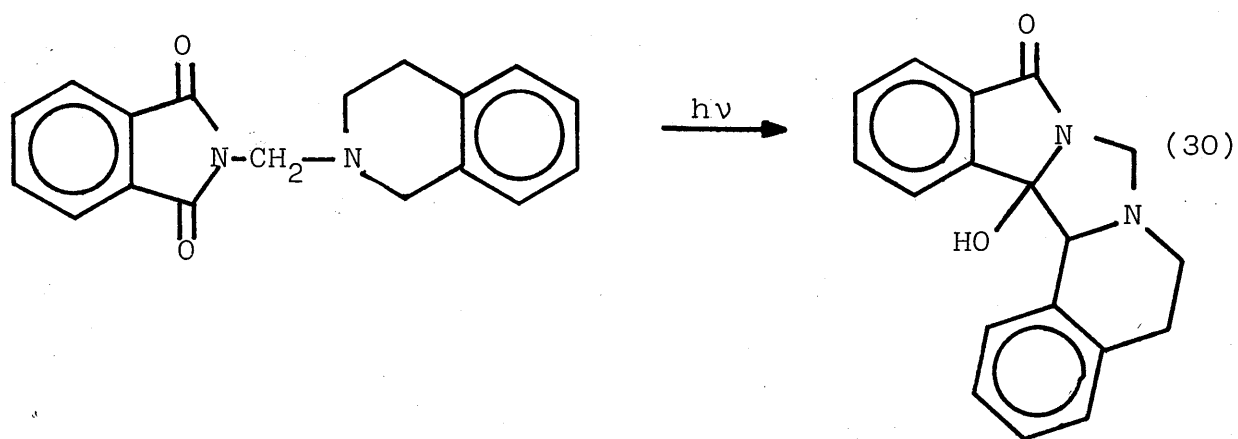
When there is no γ -hydrogen available for hydrogen transfer in the substrate, reaction can occur to give cyclic systems with different ring sizes (28).³⁷



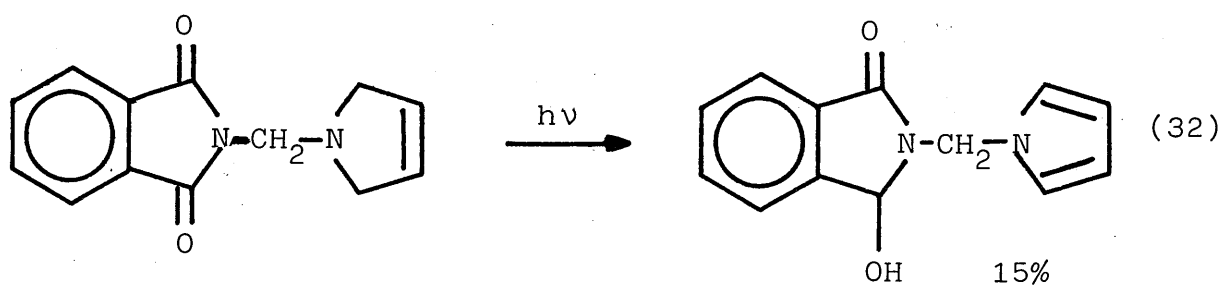
Similarly, if the γ -position is occupied by a heteroatom, substituted phthalimides give rise to products with a new 5-membered ring containing two heteroatoms (29).^{38,39}



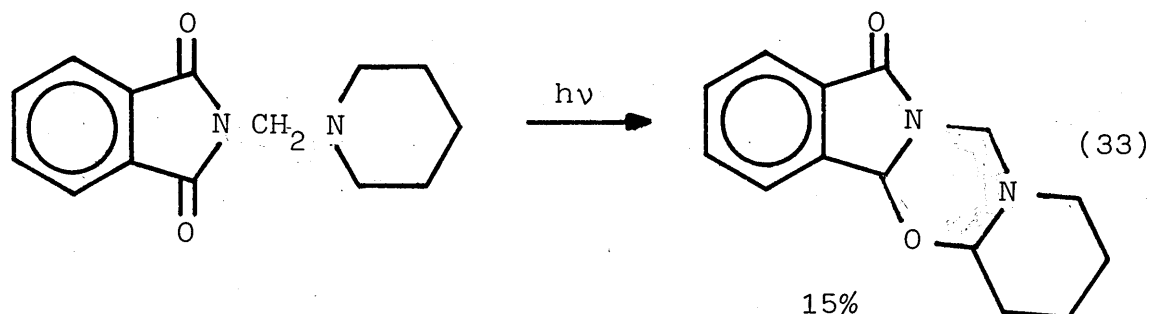
Mannich bases of phthalimide are easily prepared and on photolysis normally give good yields of fused imidazolidines as a result of reaction at the δ -position (30 and 31).⁴⁰⁻⁴²



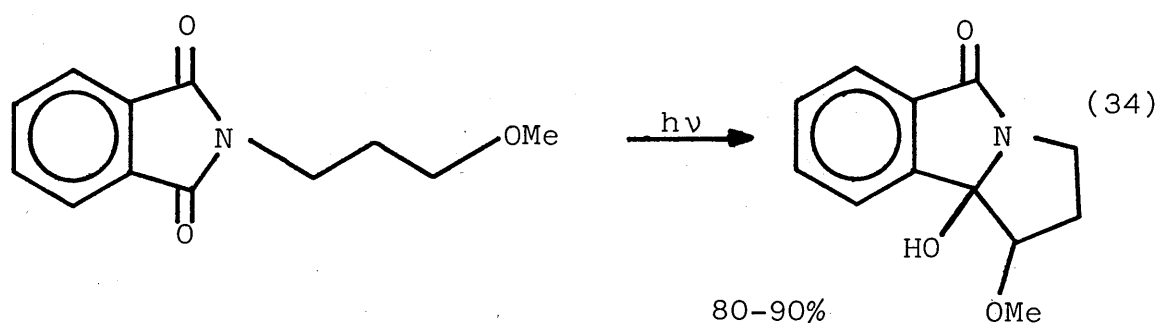
There are exceptions where an alternative reaction competes effectively with the formation of the cyclic alcohol. The Mannich base derived from 3-pyrroline⁴² gives a pyrrolomethyl substituted hydroxyisoindoline, which probably arises from the disproportionation of an intermediate biradical (32).



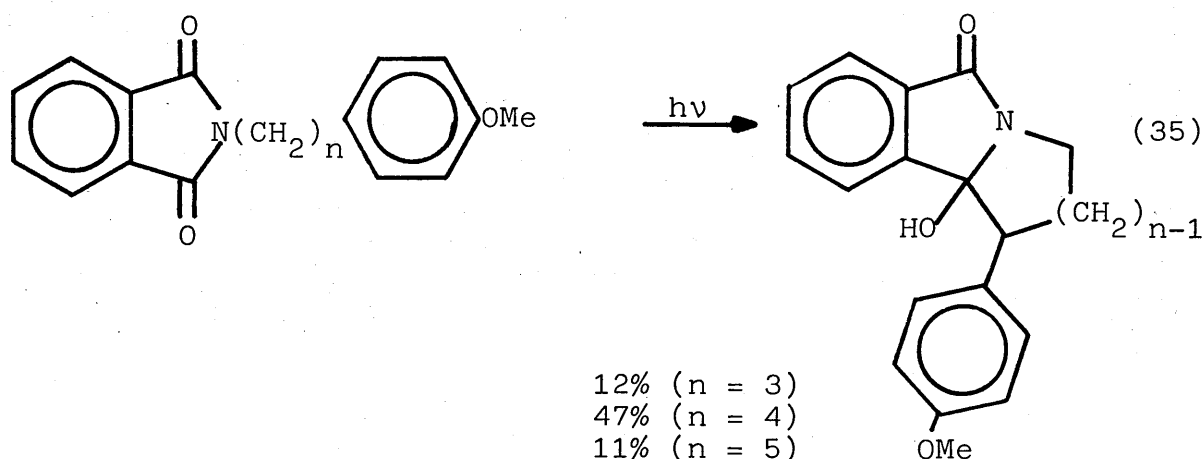
More surprising is the isolation of an oxadiazine from the Mannich base derived from piperidine (33). This might be formed by a route which involves a 1,2-hydrogen shift in a biradical.⁴⁰



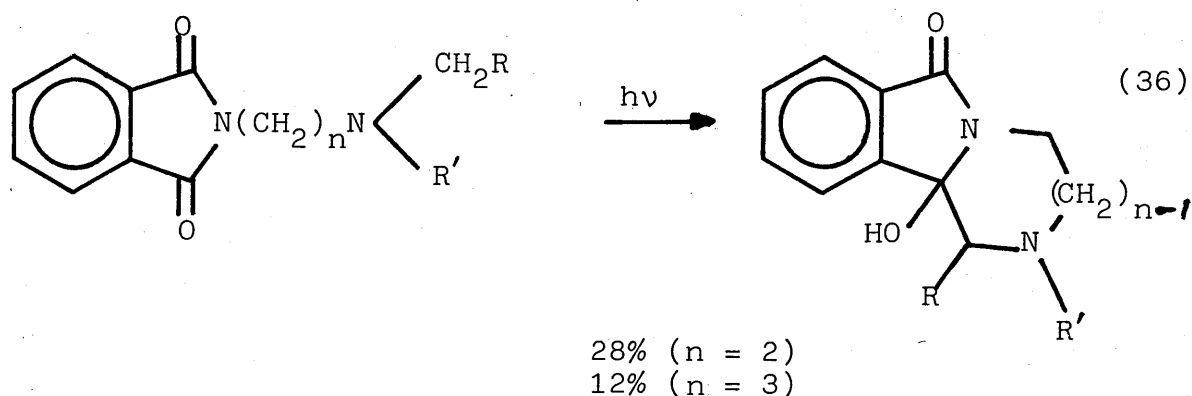
Considerable interest has been shown in systems where there is a choice of positions for hydrogen abstraction. With an oxygen atom in the side chain³⁹ there is a preference for the δ -position to take part in the reaction, provided there is the possibility of stabilising the intermediate formed in this process (34).

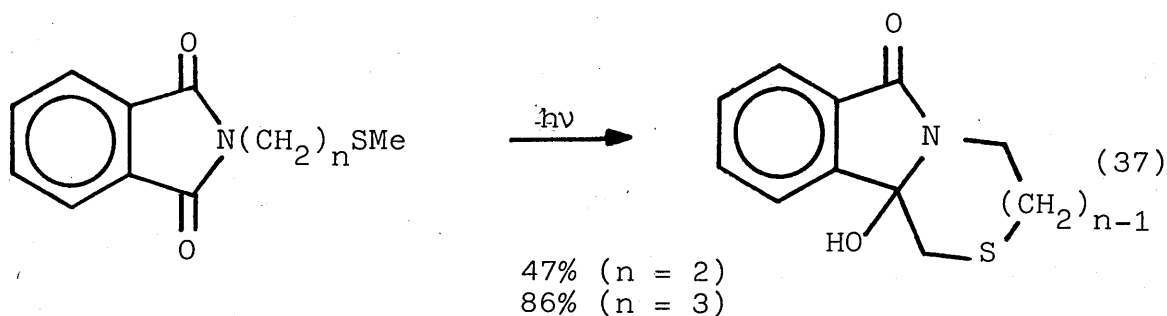


When the stabilising group is an aromatic ring,⁴³ products are formed by reaction at *5*-, *6*-, or *3*-position (35).

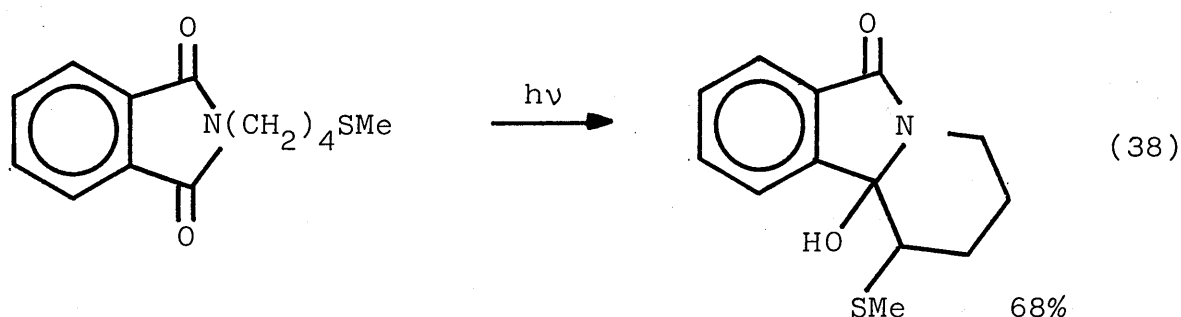


Different behaviour for nitrogen- or sulphur-containing side-chains^{44,45} is indicated by the formation of fused hexahydropyrazines and hexahydro-1,4-diazepines from aminoethyl- or aminopropyl-phthalimides (36), and the corresponding sulphur-containing ring systems are obtained from thioalkylphthalimides (37).⁴⁶

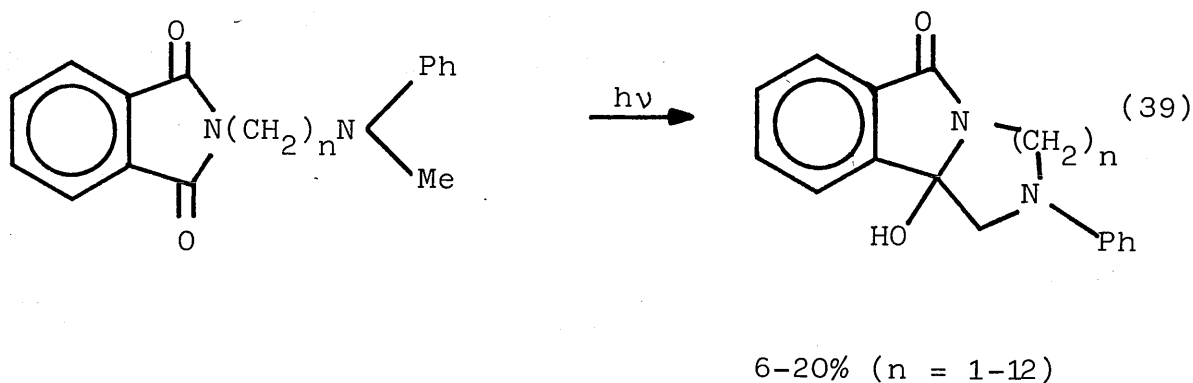


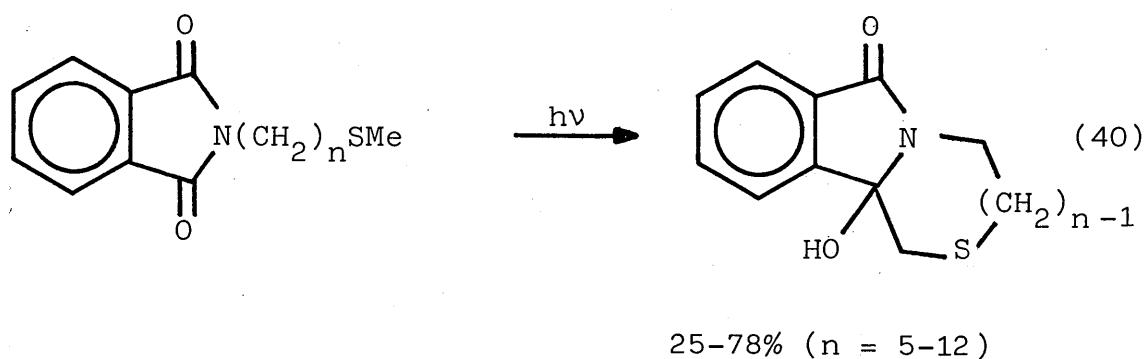


A report⁴⁶ that (4-alkylthiobutyl)phthalimides give products in which the sulphur group is exocyclic, suggested a limit to the ring sizes that could be produced in this reaction(38).

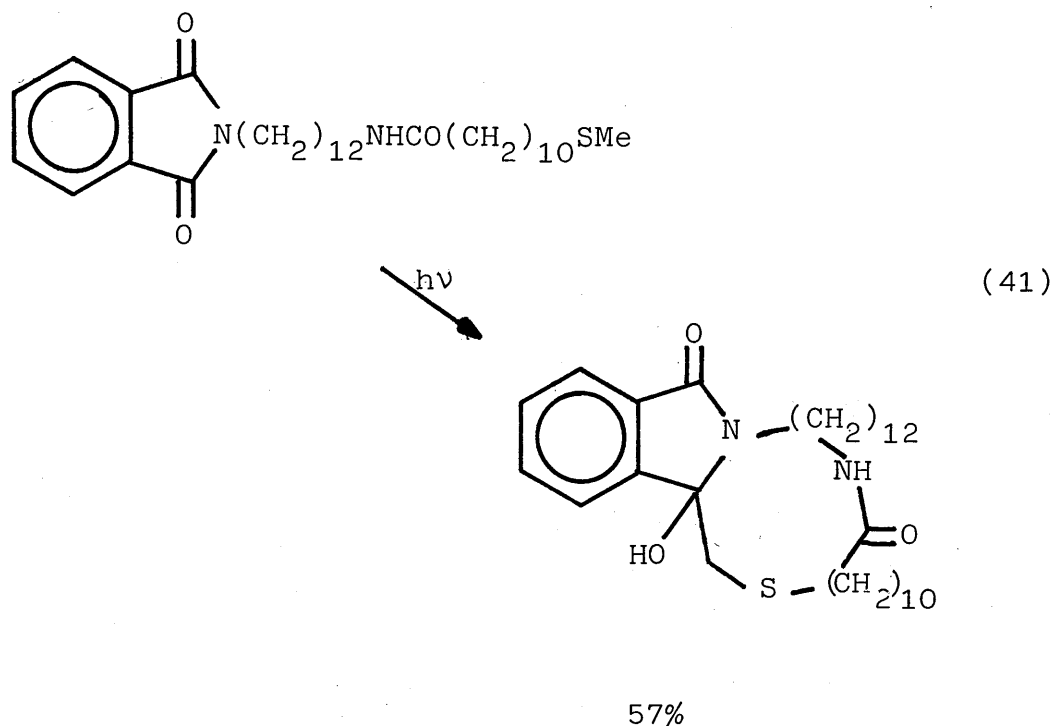


However, this was found not to be the case. Irradiation of (aminoalkyl)-⁴⁷ and (methylthioalkyl)phthalimides^{48,49} gives medium- or large-ring diaza- and thiaza-systems with ring sizes up to 16-atoms (39 and 40).





These remarkable cyclisations have been extended even further, and irradiation of phthalimides with an amide-containing or ester-containing substituent terminating in a (methylthio)- group gives macrocyclic lactams or lactones with ring sizes up to 38 atoms (41).^{50,51}

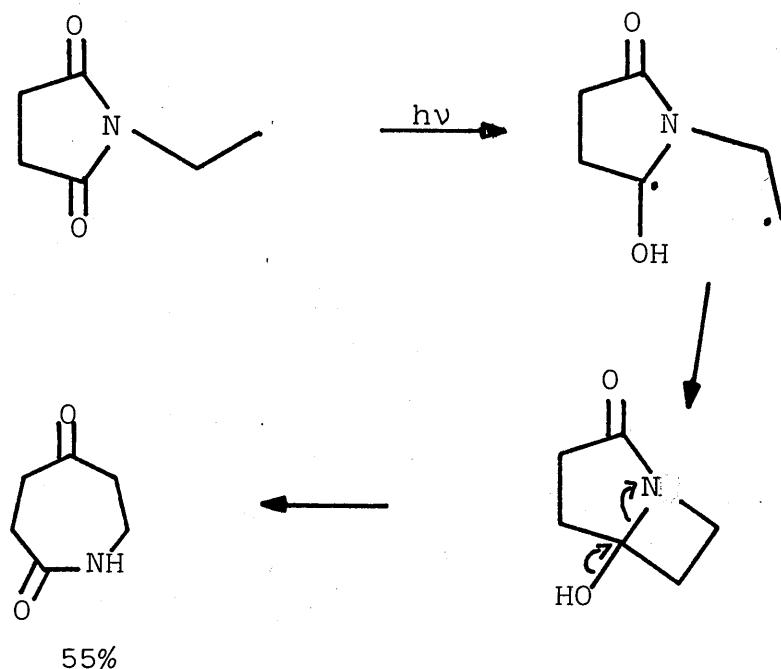


It is significant that these cyclisation reactions occur in non-rigid systems and require none of the precautions of high dilution that are associated with conventional macrocyclic synthesis. All indications

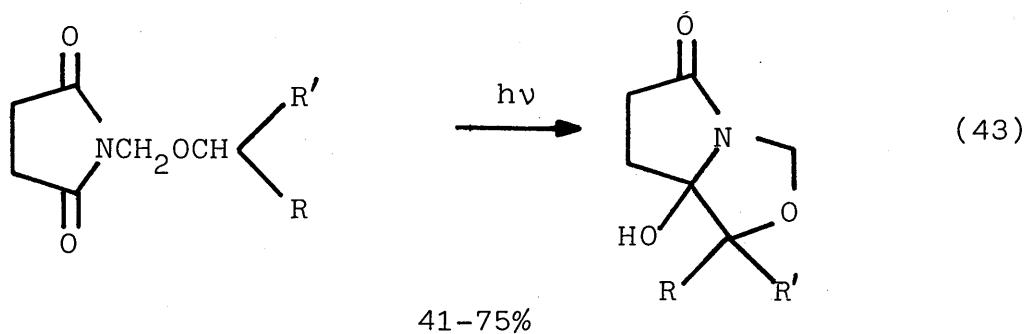
are that this reaction occurs via a charge-transfer interaction in the excited state that leads to preferential conformations in which the terminal heteroatom (δ^+) and imide (δ^-) are in close proximity.

(ii) Alicyclic imides

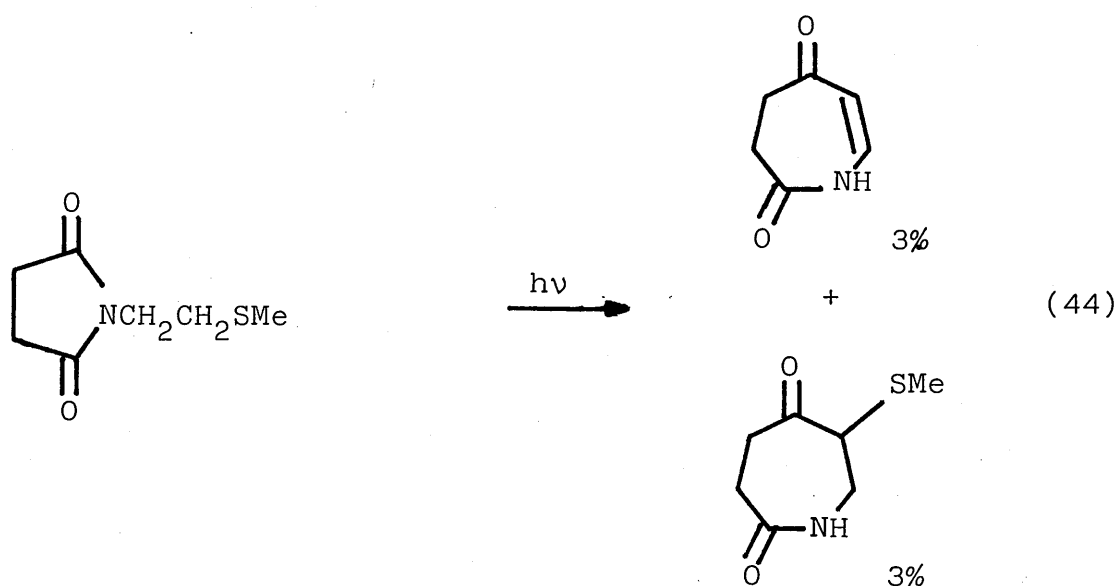
For the corresponding alicyclic imides, the most extensively studied of this series are the N-substituted succinimides.⁵²⁻⁵⁶ As with the phthalimide derivatives, N-alkylsuccinimides undergo an efficient hydrogen abstraction from the γ -position to give a biradical intermediate which affords an azepinedione via an azetidione (42).

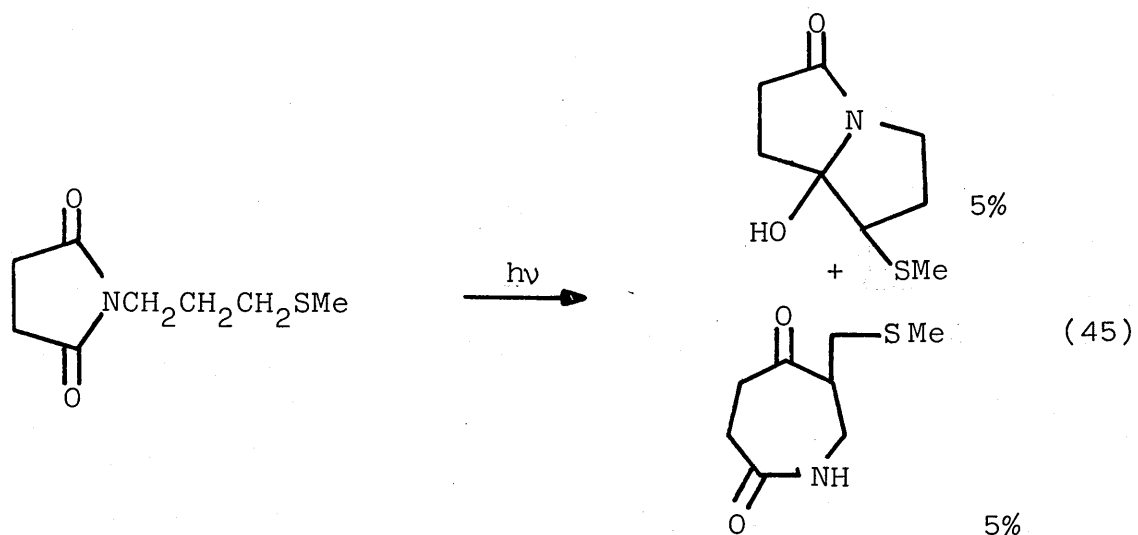


When an oxygen atom occupies the γ -position in the N-alkyl chain⁵⁷ hydrogen abstraction takes place to give a new oxazolidine ring (43).

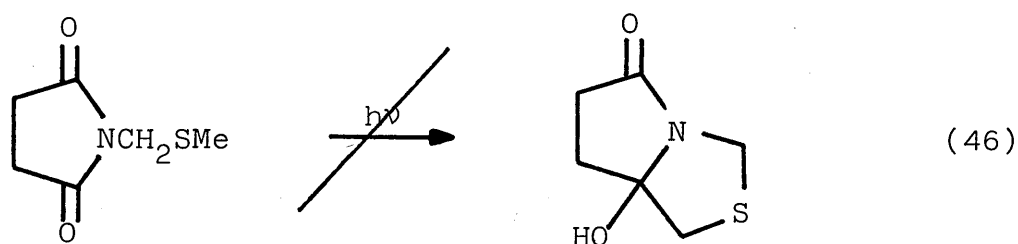


A similar reaction occurs for phthalimides (29). However, by contrast, succinimides with a sulphur atom in their side chain, show a decrease in photochemical reactivity.⁵⁷ (2-Methylthioethyl)- and (3-methylthiopropyl)-succinimide give 7-membered lactams by γ -hydrogen transfer, but in very low yields (44 and 45). Also isolated from the reaction of the thiopropyl compound was a cyclic alcohol with an exocyclic sulphur atom, formed by δ -hydrogen transfer, again in very low yield.





It has been reported⁵⁷ that (methylthiomethyl)-succinimide resists reaction upon irradiation, failing to cyclise, indicating decreased photoreactivity of the hydrogen of the δ -carbon bonded to sulphur (46).



These results show a diversion from those of the corresponding phthalimides, where the thioalkylphthalimides readily give cyclic alcohols on irradiation. The major electronic difference between aromatic and aliphatic cyclic imides is that the aromatic imide system can be a better electron acceptor.⁴⁸ This could interact favourably with a donor molecule such as a thioether, in either an intermolecular or intramolecular manner during a photoreaction. Thus, the ability of thioalkyl-

phthalimides to cyclise was recognised and utilised in the synthesis of macrocycles.^{48,50} However, aliphatic imides may not have sufficient capacity as an electron acceptor, and hence the thioether derivatives do not show the same photoreactivities in aliphatic imides, as they do in aromatic imides.

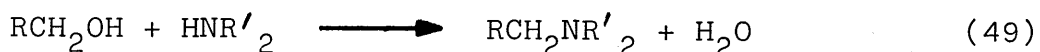
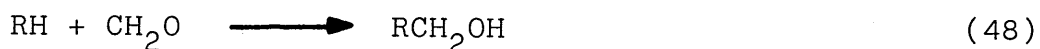
The apparent failure of the aliphatic imide systems to give photocyclisation products with the same efficiency as their aromatic counterparts led us to investigate the photochemical reactivity of N-aminoalkyl-substituted aliphatic imides, and the possibility of making polycyclic systems containing two or more nitrogen atoms. The first group of substrates we chose to study involved N-aminomethyl derivatives of alicyclic imides conveniently made by the Mannich reaction.

Although examples of the Mannich reaction had been reported earlier,⁵⁸⁻⁶¹ it was in 1917 that Mannich began a detailed investigation into what he recognised as a general reaction. Since then the reaction has been reviewed many times.⁶²⁻⁶⁴ The general reaction involves the condensation of ammonia (or a primary or secondary amine), an aldehyde (usually formaldehyde) and a compound with an active hydrogen atom (47).

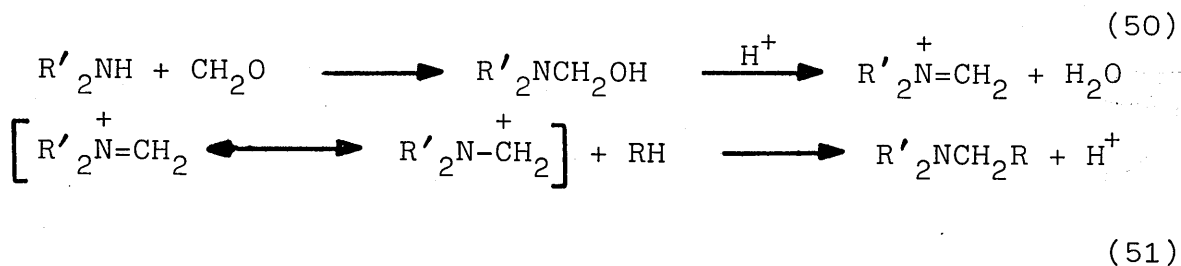


The product is known as a Mannich base. Many proposals have been put forward for the mechanism, but there seem to be two distinct reaction pathways:

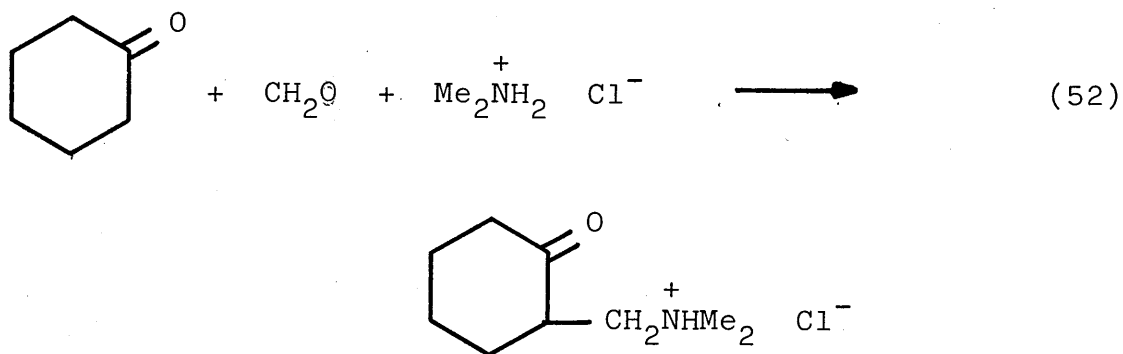
Reaction of the labile hydrogen compound with formaldehyde to give the hydroxymethyl derivative, which then condenses with the amine to produce the Mannich base (48 and 49),

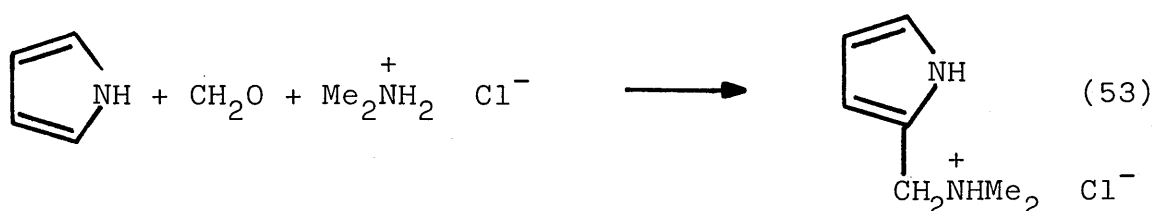


or, addition of the amine to formaldehyde to form initially an N-(hydroxymethyl)amine, and then an iminium ion which reacts with the labile hydrogen compound to produce the Mannich base (50 and 51).

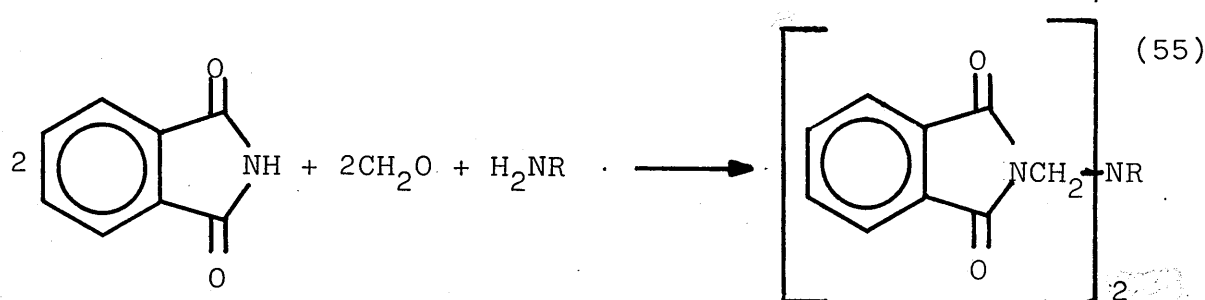
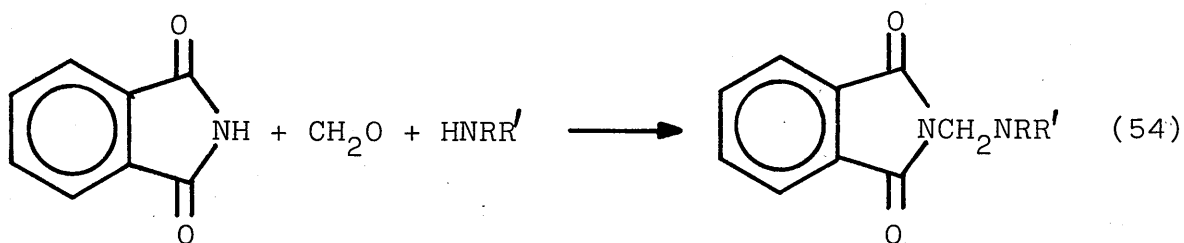


A variety of active hydrogen compounds have been used in the preparation of Mannich bases. The early work employed reactive ketomethylene compounds (52)⁶⁵ or compounds with active multiple bonded C-H (53).⁶⁶

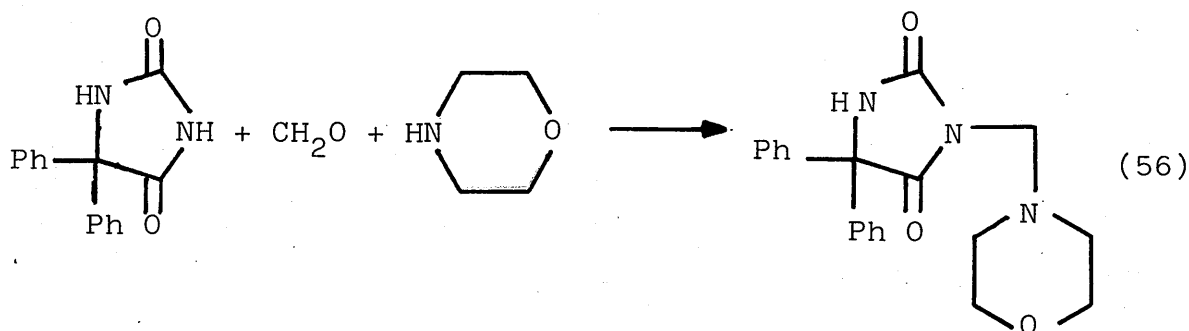




These reactions involve Mannich condensation of compounds containing an acidic hydrogen atom on carbon, but interest was also shown in the Mannich reaction of substances possessing active hydrogen on nitrogen. N-(Piperidinomethyl) and N-(morpholinomethyl) derivatives of phthalimide⁶⁷⁻⁶⁹ and succinimide^{70,71} were prepared very early on, and this type of Mannich base has been used in the identification of secondary and primary amines (54 and 55).⁷²⁻⁷⁴



Mannich bases of 5,5-diphenylhydantoin have been prepared (56),⁷⁵ as well as those of other imides or related compounds.

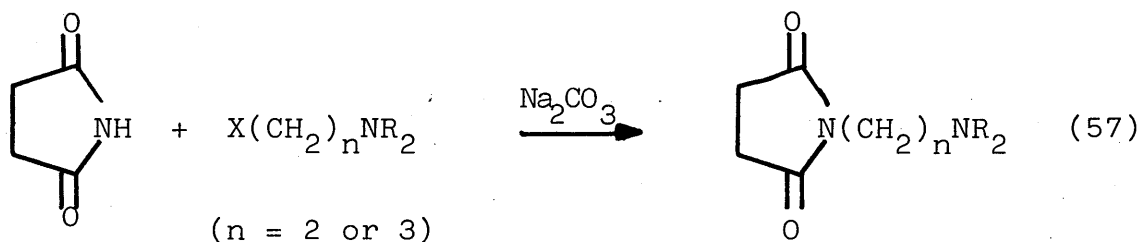


Pharmacological interest in Mannich bases was evident with, for example, papers on aminoalkylphenols as antimalarials,⁷⁶ and on the anticonvulsant activity of 2-phenylsuccinimide and its derivatives.⁷⁷⁻⁸⁰

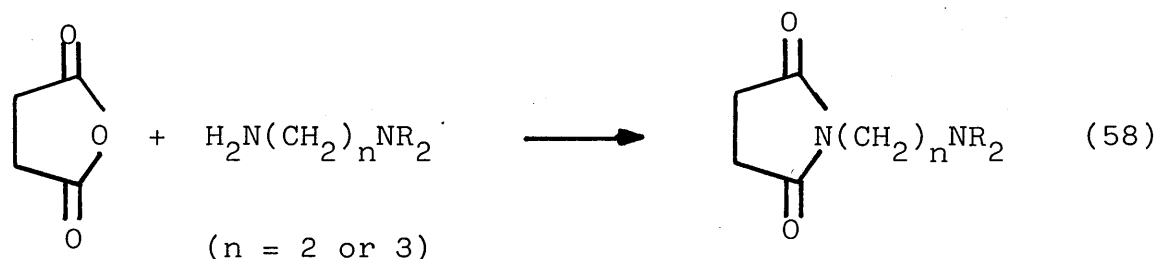
We employed the Mannich condensation of cyclic aliphatic imides to make substrates for photochemical investigation, and the imide systems we used were succinimide, 2-phenylsuccinimide, hydantoin, 5,5-diphenylhydantoin, 5,5-dimethylhydantoin, glutarimide, 3,3-dimethylglutarimide and dihydrouracil. Mannich bases derived from glutarimide, 3,3-dimethylglutarimide and dihydrouracil have not been reported previously, although derivatives of thalidomide⁸¹ and bemegride,⁸¹ which are both glutarimides, have been made. Dihydrouracil was previously reported to be unreactive in the Mannich reaction.⁸²

We were also interested in higher homologues of the Mannich bases in order to investigate whether larger ring products could be prepared photochemically. The preparation of these substrates required alternative routes. N-(2-Aminoethyl)- and N-(3-aminopropyl)-compounds

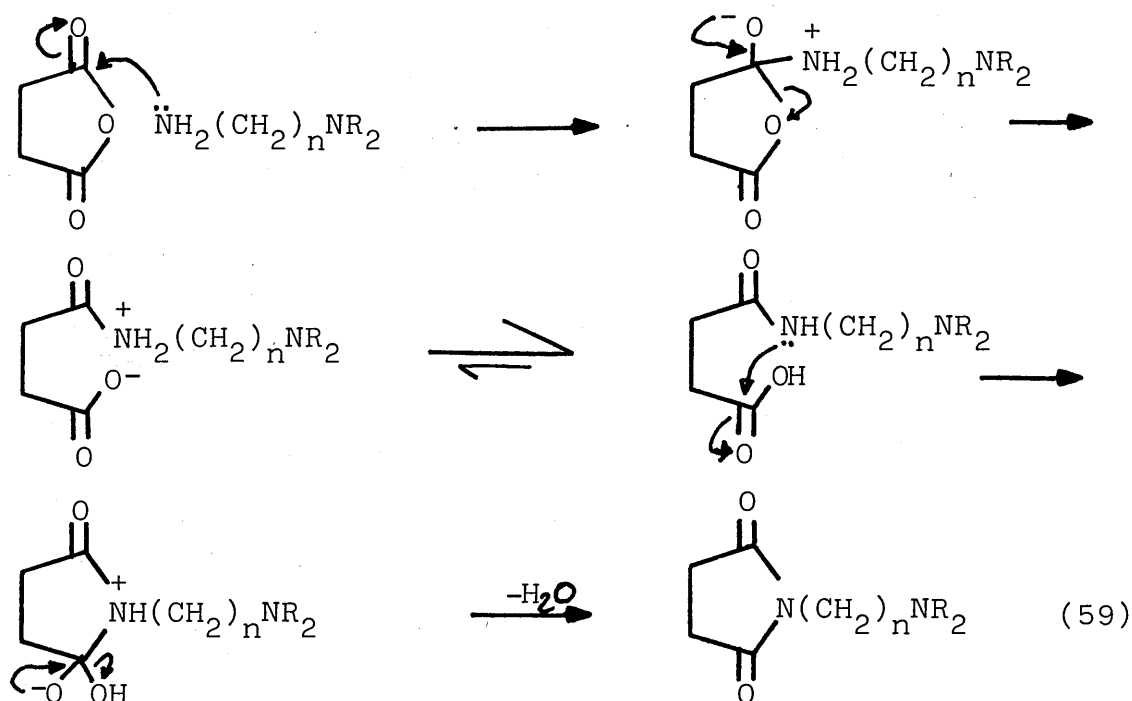
were made from the imide and haloalkylamine in the presence of base (57):



or from the anhydride and aminoalkylamine (58).

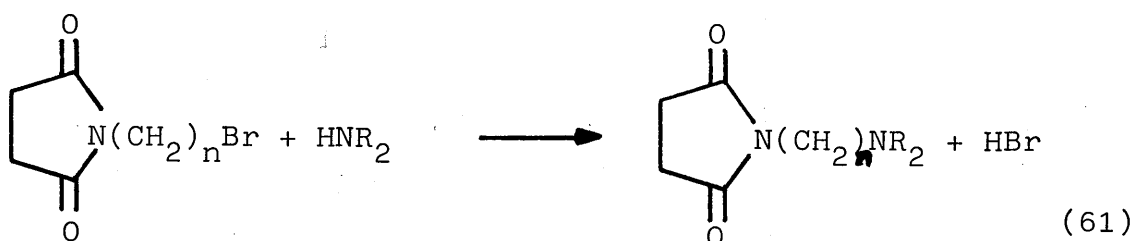
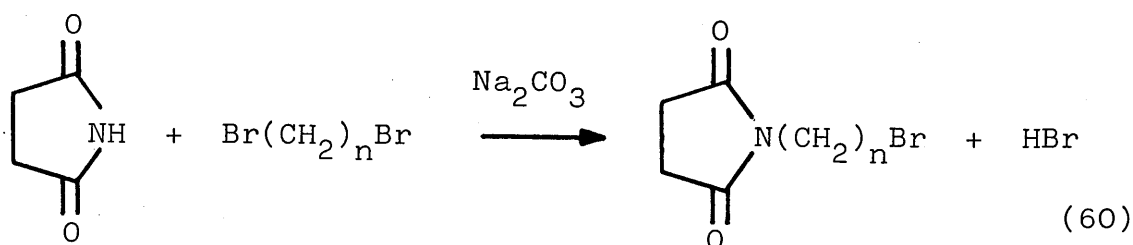


The mechanism of the reaction in (57) involves nucleophilic substitution by the imide anion. That of the reaction in (58) involves conventional nucleophilic substitution in a carboxylic acid derivative (59).



The choice of procedure was dependent on the availability of materials, except in the case of substituted maleimides, which had to be prepared by the first route, because nucleophilic addition of an amine to the conjugated alkene part of the imide competes in the second route.

N-(4-Aminobutyl) compounds, and higher homologues, were prepared by reaction of a dibromoalkane (in excess) with the imide in the presence of base, and then subsequent nucleophilic substitution by a secondary amine in the (bromoalkyl)imide (60 and 61).



The preparation of substrates, their photochemical reactions and the identification of photoproducts are described in chapters 2,3 and 4 according to three basic imide systems:- saturated 5- or 6-membered cyclic imides (chapter 2), hydantoins and dihydrouracils (chapter 3) and maleimides (chapter 4).

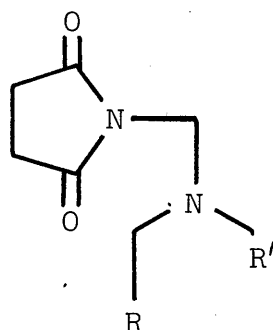
C H A P T E R T W O

THE RESULTS AND DISCUSSION FOR THE SUCCINIMIDE
AND GLUTARIMIDE DERIVATIVES

Our interest lies in the application of photochemical cyclisation processes to the synthesis of heterocyclic compounds, and the apparent failure of some N-substituted aliphatic imide systems to give photocyclised products with the same efficiency as their aromatic counterparts, led us to investigate the photochemical reactivity of N-aminoalkyl substituted aliphatic imides. This chapter contains the results and discussion for succinimide and glutarimide derivatives, dealing with Mannich bases first, and then the higher homologues.

N-(Dialkylaminomethyl) derivatives (Mannich bases)

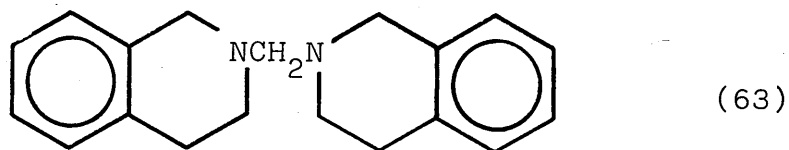
Mannich bases of succinimide with formaldehyde and a secondary amine are easily prepared in ethanol solvent^{63,70,71} and most are crystalline solids which readily precipitate from the reaction mixture. Those products which are not solids can be isolated either by silica-gel column chromatography or by the preparation of the crystalline hydrochloride salt. The Mannich base is regenerated from the salt by neutralisation with an aqueous solution of sodium bicarbonate. The Mannich bases prepared and the yields obtained are listed below:



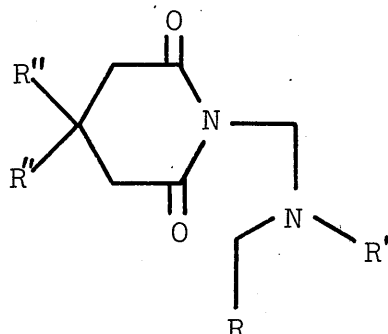
(62)

(a) R, R' = CH ₂ OCH ₂ CH ₂	81%
(b) R, R' = (CH ₂) ₄	77%
(c) R = CH=CH ₂ ; R' = CH ₂ CH=CH ₂	72%
(d) R = CH ₃ ; R' = CH ₂ CH ₃	58%
(e) R, R' = CH=CHCH ₂ CH ₂	47%
(f) R, R' = o-C ₆ H ₄ CH ₂ CH ₂	71%
(g) R = Ph; R' = CH ₂ Ph	61%
(h) R = Ph; R' = CH ₃	72%
(i) R = H; R' = CH ₃	65%

Mannich bases from glutarimide, however, are not as easily prepared, and we have found only two previous examples in the literature which dealt with specific pharmacologically active compounds, bemegride⁸¹ and thalidomide.⁸¹ Attempted preparation of glutarimide compounds by the same method employed for the succinimide Mannich bases usually gave recovered glutarimide. A bis(amino)methane (63) was also isolated when 1,2,3,4-tetrahydroisoquinoline was employed as the secondary amine.



To overcome this problem, we modified the preparation by excluding solvent, and adding glutarimide to 100% excess of amine and formaldehyde. Warming the reaction mixture formed a homogeneous solution, and when cooled a solid precipitated, which was filtered and recrystallised. The Mannich bases of glutarimides and the yields obtained are listed below:



(a) $R'' = H$; $R, R' = CH_2OCH_2CH_2$	42%
(b) $R'' = H$; $R, R' = o-C_6H_4CH_2CH_2$	67%
(c) $R'' = H$; $R, R' = CH=CHCH_2CH_2$	61%
(d) $R'' = H$; $R, R' = (CH_2)_4$	49%
(e) $R'' = CH_3$; $R, R' = CH_2OCH_2CH_2$	47%
(f) $R'' = CH_3$; $R, R' = o-C_6H_4CH_2CH_2$	61%
(g) $R'' = CH_3$; $R, R' = CH=CHCH_2CH_2$	57%
(h) $R'' = CH_3$; $R, R' = (CH_2)_4$	51%

A number of spectral properties are characteristic of the Mannich bases. In the infrared spectra there are two carbonyl stretching bands at ~ 1700 and 1770

cm^{-1} for succinimides, or at ~ 1670 and 1730 cm^{-1} for glutarimides, which are also observed for the unsubstituted imides. The NCH_2N group in the Mannich bases gives rise to signals in the proton and carbon magnetic resonance spectra at ~ 4.5 and ~ 60 ppm respectively.

In the carbon magnetic resonance spectra there is only one carbonyl signal, at ~ 180 ppm for succinimides and ~ 175 ppm for glutarimides, which again corresponds to the signal observed for the unsubstituted imide.

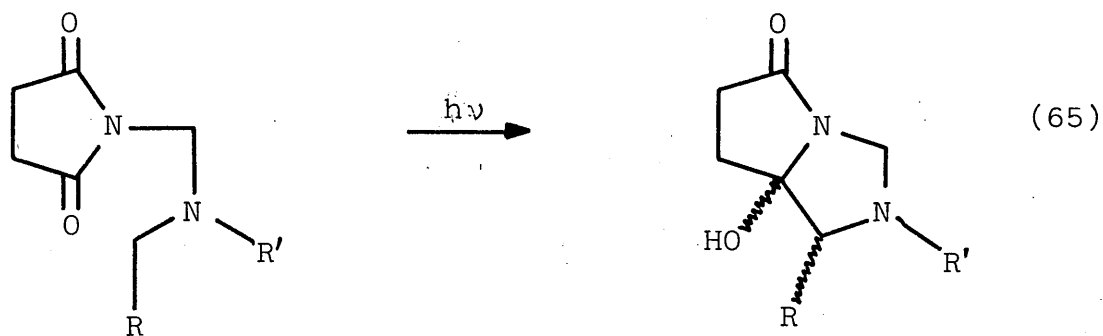
These Mannich bases are not able to give azepinediones or azocinediones on irradiation, as N-alkylimides do (42); this is because the γ -position is occupied by a nitrogen atom. However, (62) and (64) could give rise to photocyclised products by reaction at the position adjacent to the nitrogen atom, i.e. the δ -position.

The most suitable wavelength of light required to irradiate the Mannich bases was determined from their ultraviolet spectra. The ultraviolet absorption spectra show a weak absorption at $\sim 240 \text{ nm}$ ($\epsilon = 400 \text{ l mol}^{-1} \text{ cm}^{-1}$) which tails off at $\sim 270 \text{ nm}$. A low-pressure mercury arc produces most of its uv output at 254 nm , and is ideal for the irradiation of these compounds. However, the output of our low-pressure mercury lamp was quite small, ~ 0.5 watts at 254 nm ,⁸³ and the reaction times required for a sample of ~ 0.02 mol Mannich base were over 100 hours. Although the main wavelengths of light emitted from a medium-pressure mercury lamp

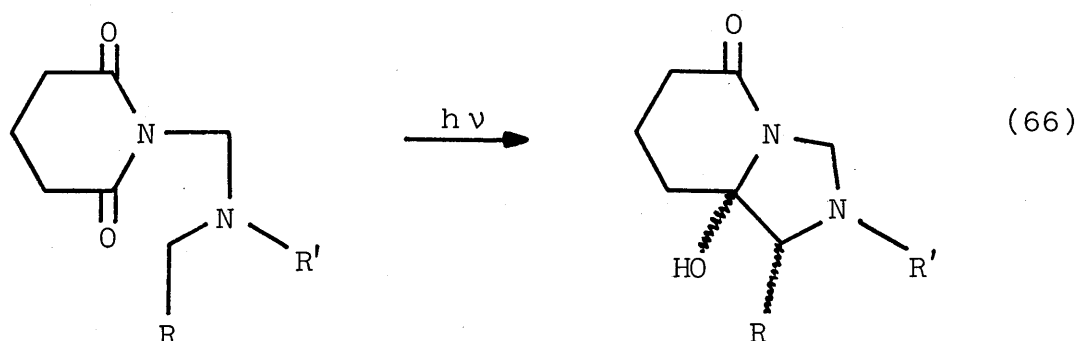
are above 300 nm, a 400-watt lamp is stated to give a total output of ~ 5.5 watts at 254 nm.⁸⁴ Using such a lamp, reaction times for a sample of ~ 0.02 mol Mannich base were typically 8 hours.

Acetonitrile was used as solvent for the irradiations, and was chosen because the substrates were soluble in it, and because it does not absorb the light emitted by the mercury arc. Irradiations were first carried out on an analytical scale (a solution containing ~ 0.002 mol Mannich base), and then repeated on a preparative scale (a solution containing ~ 0.02 mol Mannich base). The reactions were monitored by thin-layer chromatography (T.L.C.).

Irradiation of the symmetrical N-(dialkylaminomethyl) derivatives (62a, b, c, d and 64a) usually gave two major photoproducts (in 7 - 77% combined yields based on unrecovered starting material) which could be separated by silica-gel column chromatography. These major photoproducts are two diastereoisomeric compounds with a new imidazolidine ring (65 and 66).



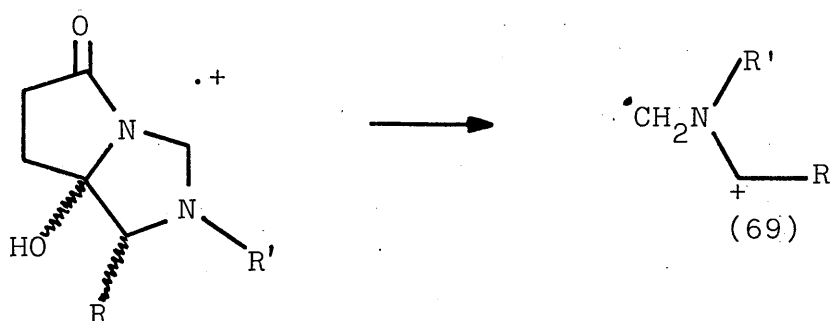
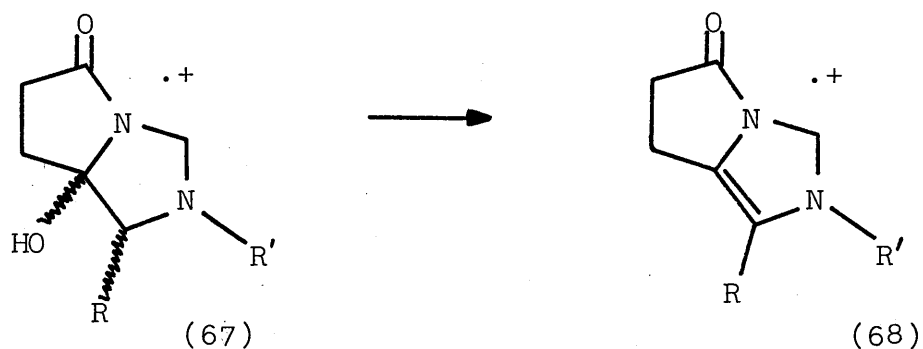
(a) R, R' = CH ₂ OCH ₂ CH ₂	77%
(b) R, R' = (CH ₂) ₄	46%
(c) R = CH=CH ₂ , R' = CH ₂ CH=CH ₂	46%
(d) R = CH ₃ ; R' = CH ₂ CH ₃	7%
(e) R, R' = CH=CHCH ₂ CH ₂	68%
(f) R, R' = o-C ₆ H ₄ CH ₂ CH ₂	51%



(a) R, R' = CH ₂ OCH ₂ CH ₂	12%
(b) R, R' = o-C ₆ H ₄ CH ₂ CH ₂	36%

The structures of the photoproducts were assigned on the basis of microanalytical results and spectroscopic properties. The elemental analysis results showed that the photoproducts are isomers of the Mannich bases. In some cases, elemental analysis did not give good results, due to the difficulty in purifying small quantities of semi-solids and gums, so high-resolution mass spectra were obtained for these samples. The

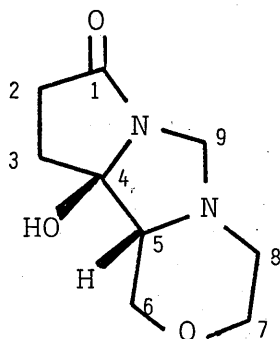
mass spectra usually gave a molecular ion (M^+ , 67) a loss of water peak ($M^+ - H_2O$, 68) and a base peak corresponding to the radical ion (69). These last two peaks can most easily be accounted for on the basis of the photocyclised structure.



Other spectroscopic properties of the photoproducts support the structural assignment as diastereoisomers of 1,3-diazabicyclo[3.3.0]octanes and 1,8-diazabicyclo[4.3.0]nonanes from succinimide and glutarimide Mannich bases respectively.

The infrared spectra show an absorption band at ~ 3300 cm^{-1} (usually broad) for the hydroxyl group, and a single lactam carbonyl is indicated by a strong band at ~ 1700 cm^{-1} for the diazabicyclo-octanes, and ~ 1610 cm^{-1} for the diazabicyclo-nonanes. The most characteristic feature of the ^1H -nmr spectra is a pair of doublets at $\sim 5.0 - 4.2$ and $4.4 - 3.4$ ppm arising from the NCH_2N system of the imidazolidine ring. These doublets arise because the hydrogen atoms are in a ring and are non-equivalent magnetically.

In general, the remainder of the ^1H -nmr spectra recorded on a 90 MHz instrument are very complex and assignment of the signals is very difficult. We have obtained medium-field (220 MHz) ^1H -nmr spectra for the isomers of (65 a) and have attempted to assign the signals for the isomer with the bridgehead OH and H groups cis (see page 48) using molecular models to estimate coupling constants.



(70)

4.38	d, J=6 Hz, 1H
4.16	dd, J=11 and 3/4 Hz, 1H
3.88	dm, J=11 Hz, 1H
3.79	d, J=6 Hz, 1H
3.7 - 3.5	m, 3H, including dd, J= 11 and 3Hz, broad signal, could include signals with J=10 Hz
3.2 - 2.9	m, 2H, could include signals with J=17 Hz, and J=10 Hz
2.58	td, J=11 and 3/4 Hz, 1H
2.45	ddd, J=17, 7/8 and 4 Hz, 1H
2.33	dd, J=9/10 and 3 Hz, 1H
2.19	m, 2H, could include signals with J=10 and 3/4 Hz, and J=10 and 7 Hz

Although a lot of the assignment must be regarded as tentative, we can be fairly certain that the pair of doublets at 4.38 and 3.79 ppm arises from hydrogens 9 and 9', and the multiplet at 2.19 ppm corresponds to hydrogens 3 and 3'. The upfield shift for 3 and 3' from ~2.7 ppm in succinimide is due to the absence of the adjacent carbonyl group in the photoproduct.

The coupling constants in this multiplet include 10 and 3/4, and 10 and 7 Hz, therefore 10 Hz is likely to be the geminal coupling constant and this suggests that for the signals for the adjacent methylene hydrogen atoms 2 and 2', one would have a coupling constant of 3/4 Hz and the other 7 Hz. It seems necessary to assume that the succinimide-derived ring is slightly distorted so that one hydrogen atom 3 is at $\sim 90^\circ$ to an adjacent hydrogen atom 2, which would give rise to a very small coupling constant. The signal at 2.45 ppm (ddd, J=17, 7/8 and 4 Hz) could correspond to the other hydrogen atom 2'; 17 Hz is the geminal coupling constant, 7/8 Hz the cis coupling constant and 4 Hz the trans coupling constant. Therefore, the hydrogen atom 2 would have only geminal (17 Hz) and cis (7/8 Hz) coupling constants. The multiplet at 3.2 - 2.9 ppm could include a signal with J=17 Hz, and we have designated this 2.

The other signals of the spectrum all contain a coupling constant of approximately 9 - 11 Hz. Therefore, we have attempted to assign some of them on the basis of chemical shift values.

The doublet of doublets signal at 4.16 ppm and the similar signal in the multiplet at 3.7 - 3.5 ppm we have assigned to hydrogen atoms 6 and 6' (adjacent to oxygen), and these hydrogen atoms are coupled with the hydrogen atom 5, which could be assigned to the doublet of doublets at 2.33 ppm. Against this assignment, however, the appropriate coupling constants are not

exactly the same, and the chemical shift value of 2.33 ppm seems too low - we might expect it to be nearer 3.0 ppm, based on the fact that the corresponding methine hydrogens of the photoproducts (65 e and 65 f) give rise to signals at 3.66, and 4.33 and 3.61 ppm respectively, and the methylene hydrogen atoms adjacent to the amine nitrogen atom of N-(morpholin-4-ylmethyl)succinimide (62 a) resonate at \sim 2.5 ppm.

The remaining unassigned signals should correspond to hydrogen atoms 7, 7', 8 and 8', and we would predict that the signals for the methylene hydrogen atoms adjacent to oxygen, 7 and 7', should be at lower field than the signals for the methylene hydrogen atoms adjacent to nitrogen, 8 and 8'. Hence, we assign the doublet of multiplets at 3.88 ppm and one hydrogen of the multiplet at 3.7 - 3.5 ppm to 7 and 7', and one hydrogen of the multiplet at 3.2 - 2.9 ppm and the triplet of doublets at 2.58 ppm to 8 and 8'.

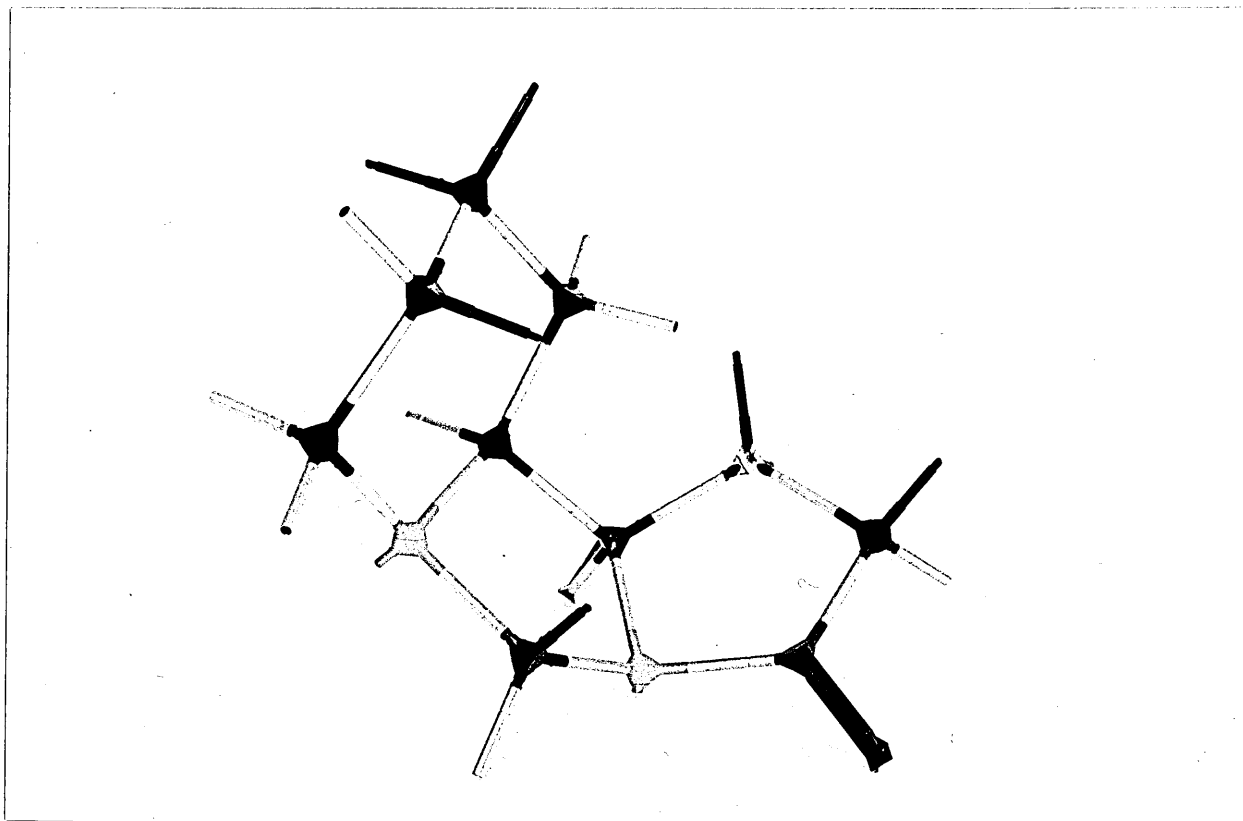
It must be remembered that this is only a tentative assignment, and it would be useful to undertake some selective decoupling experiments to enable us to identify which signals are coupled to one another.

The large difference in the ^1H -nmr chemical shift values for the hydrogen atoms of the NCH_2N group (typically 0.6 to 1.1 ppm for both isomers of (65 a and 65 b) could be attributed to effects caused by the hydroxyl group, the lone pairs of the nitrogen atoms or the carbonyl group. We suspect that the same hydrogen

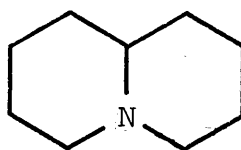
atom in both stereoisomers is shielded and shifted upfield to 3.36 - 3.79 ppm (the singlet for the NCH_2N hydrogen atoms in succinimide or glutarimide Mannich bases is typically 4.5 ppm). If this assumption is correct the effect of the hydroxyl group can be ruled out as it would affect different hydrogen atoms in the two stereoisomers.

An effect by either the carbonyl group or the lone pairs of the nitrogen atoms is plausible. Molecular models of our photoproducts indicate that one particular hydrogen atom of the NCH_2N group is always in a region above the plane of the carbonyl group independent of the stereochemistry (plate 1). Hence this hydrogen might give a signal at higher field in the ^1H -nmr spectrum, due to the shielding effect in this zone above the plane of the carbonyl group.⁸⁵ The magnitude of this shielding cannot be estimated because there are insufficient spectral data for model compounds, and hence we cannot rule out the effect of the carbonyl group.

A shielding effect on the other hydrogen atom in both stereoisomers by the lone pairs of the nitrogen atoms would require that the two lone pairs are always on the same side of the molecular plane (syn). Otherwise, if the amine nitrogen atom is able to invert so that the lone pairs are on opposite sides of the molecular plane (anti) both hydrogen atoms should experience a shielding effect. (We feel that the amide nitrogen atom will not invert due to the severe strain in the



trans-diazabicyclo[3.3.0]nonane system). It has been shown^{86 - 88} that there is a large chemical shift difference (0.92 ppm) between the geminal hydrogens adjacent to nitrogen in the ¹H-nmr spectrum of quinolizidine (71), and this has been ascribed to the effect of the axial lone pair of electrons on nitrogen shielding the axial protons in the adjacent methylene groups. Similar large differences have also been observed in other nitrogen-containing heterocycles of fixed conformation containing axial lone pairs.^{89, 90}



(71)

Molecular models of the photoproducts derived from saturated cyclic amines (65 a) and (65 b) indicate that the lone pairs of the nitrogen atoms can be syn or anti without undue strain. For the isomer with the relevant OH/H groups cis with respect to each other (plate 2), syn lone pairs are accommodated in a flexible structure, whereas for the isomer with the OH/H groups trans (plate 3), the conformation with syn lone pairs gives a rigid molecule. In the more rigid structure the effect of the lone pairs is likely to be greater than for the more flexible structure, and hence we can tentatively assign the spectral data with the greatest difference in chemical shift value for the hydrogen atoms of the NCH_2N group to the isomer with the relevant OH/H groups trans with respect to each other.

The effects observed when the photoproduct is derived from an unsaturated acyclic amine (65 c) are the same as for the saturated cyclic amines. However, for photoproducts derived from unsaturated cyclic amines (65 e and 65 f) that have an alkene or aromatic group adjacent to the methine group, the chemical shift difference between the hydrogen atoms of the NCH_2N group in both isomers is much less than in the previous examples. These results are discussed later (page 57).

To test our hypothesis that the observed chemical shift differences arise from the effect of syn lone pairs of electrons on nitrogen in the photoproducts, it is suggested that ^1H -nmr studies be carried out on the single isomer of the photoproduct from N-(dimethyl-

PLATE 2

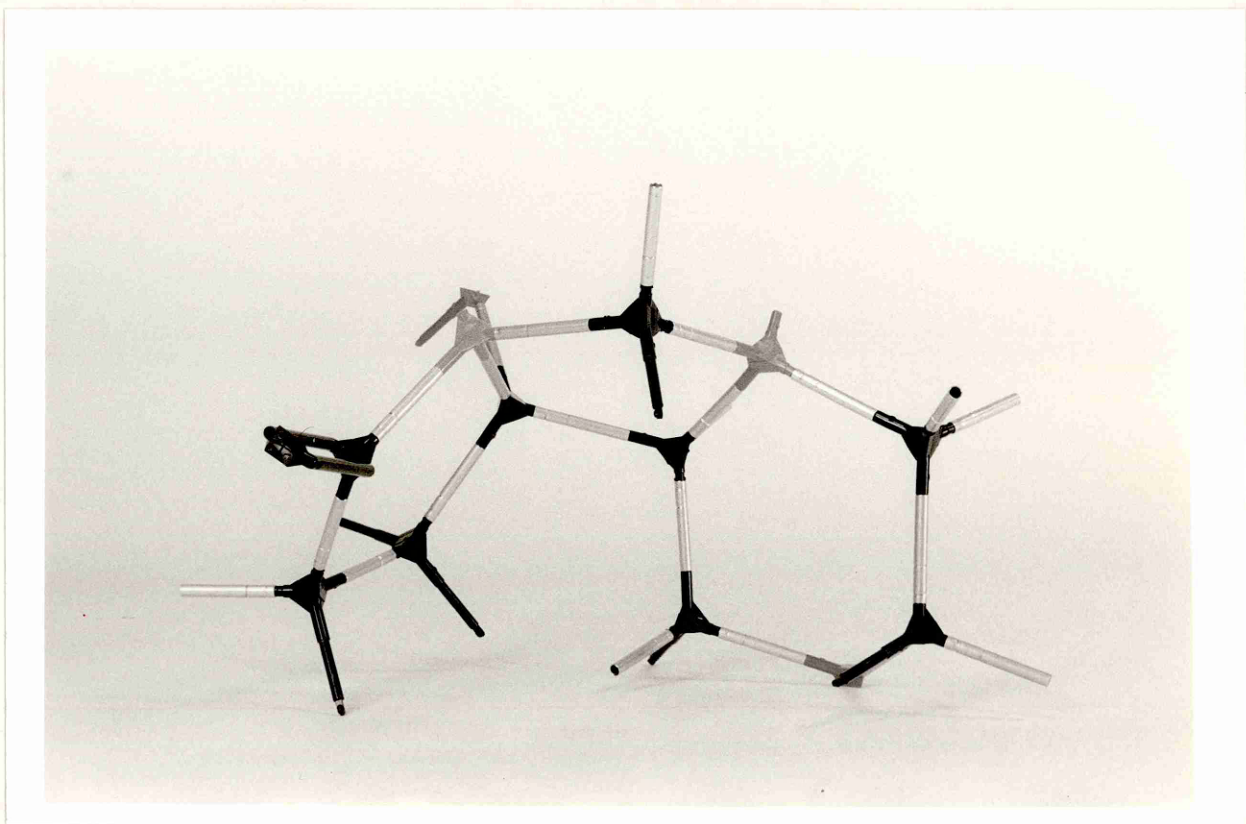
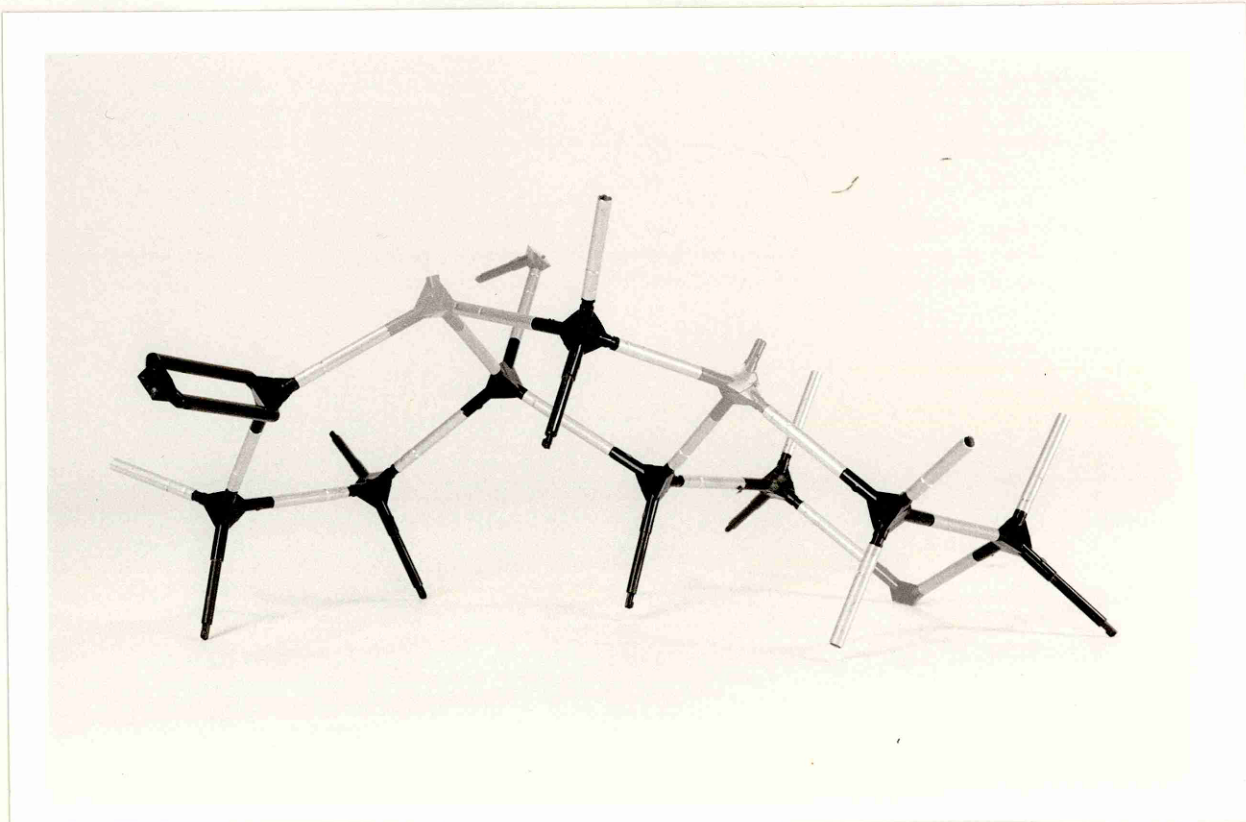
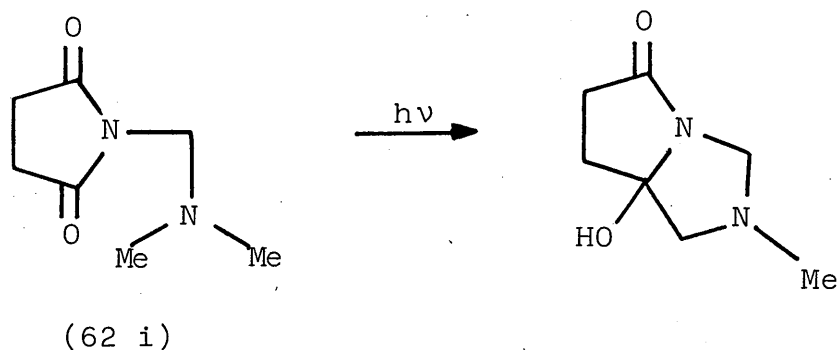


PLATE 3



aminomethyl)succinimide (62 i).



We would predict that at room temperature the separation of the signals for the hydrogen atoms of the NCH_2N group would be small due to rapid inversion of the amine nitrogen atom, and hence a shielding of both hydrogen atoms. (This is found to be the case with the photoproducts (82 and 83) from N-(dimethylaminomethyl)-2-phenylsuccinimide, see page 70). Low-temperature ^1H -nmr studies, at a temperature where the rate of inversion is slower than the nmr time scale, should give a spectrum where four doublets are observed for the hydrogen atoms of the NCH_2N group, assuming that one conformation is not significantly more favourable thermodynamically than the other.

Another effect that we observe in the ^1H -nmr spectra of the photoproducts is a difference in the coupling constants between the geminal hydrogen atoms of the NCH_2N group for the stereoisomers of (65 a, b, c, e, f and 66 b). We believe that the smaller coupling constants could arise because of steric compression in the cis isomer. This would tend to increase the

internal bond angles of the imidazolidine ring and decrease the geminal angle between the hydrogen atoms of the NCH_2N group, resulting in a decrease in coupling constant. Steric compression leading to bond lengthening has been shown⁹¹ to decrease the chemical shift value in the ^{13}C -nmr spectrum of one or both of the carbon atoms linked by the lengthened bond. We have observed this effect in the ^{13}C -nmr spectra of the photoproducts (65 a, b, c, e, f and 66 b) where the signal for the quaternary carbon atoms (C-OH) in the cis isomer has a lower chemical shift value than in the trans isomer.

The ^{13}C -nmr spectra also show a lower chemical shift value for the amide carbonyl carbon atom in the cis isomer. This could be due to the amide nitrogen atom becoming more planar in this isomer in order to relieve some of the steric strain. This seems reasonable when comparing the chemical shift values in the ^{13}C -nmr for the amide carbonyl carbon atom in succinimide photoproducts (trans isomers ~ 180 and cis isomers ~ 175 ppm) with pyrrolidin-2-one (~ 175 ppm).

We can therefore rationalise the ^1H -nmr and ^{13}C -nmr spectral data for the stereoisomers of the photoproducts. To summarise the results and hypotheses, the isomers with the OH/H group cis:-

1. Exhibit a smaller ^1H -nmr chemical shift difference for the hydrogen atoms of the cyclic NCH_2N group, because the greater flexibility of the ring system affects the spatial relationship to the nitrogen lone

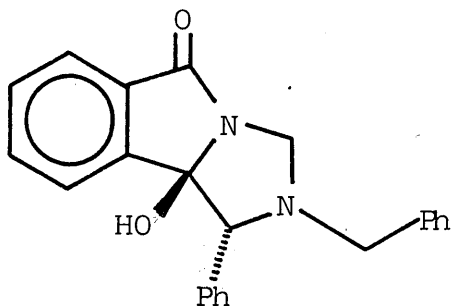
pairs.

2. Show a smaller geminal coupling constant for the hydrogen atoms of the cyclic NCH_2N group due to steric compression of the rings leading to a decrease in the geminal angle.

3. Have a lower ^{13}C -nmr chemical shift value for the quaternary carbon atom (C-OH) due to steric compression resulting in bond lengthening.

4. Have a lower ^{13}C -nmr chemical shift value for the amide carbonyl carbon atom because the amide nitrogen atom is more planar.

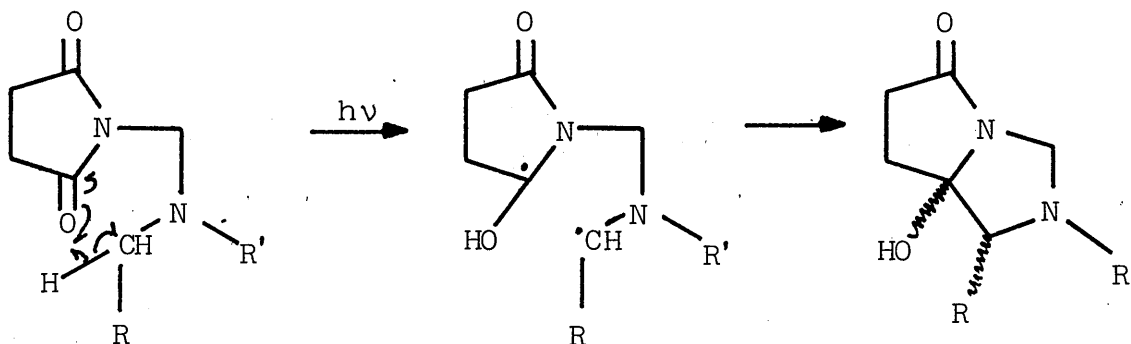
These hypotheses are plausible and consistent with the spectroscopic results obtained, and they are in keeping with spectral data for a series of phthalimide photoproducts⁹² where definite structural assignment has been made for cis-4-benzyl-2-hydroxy-3-phenyl-4,6-diazatricyclo[6.4.0.0^{2,6}]dodeca-8,10,12-trien-7-one (72) by X-ray crystallographic analysis.



(72)

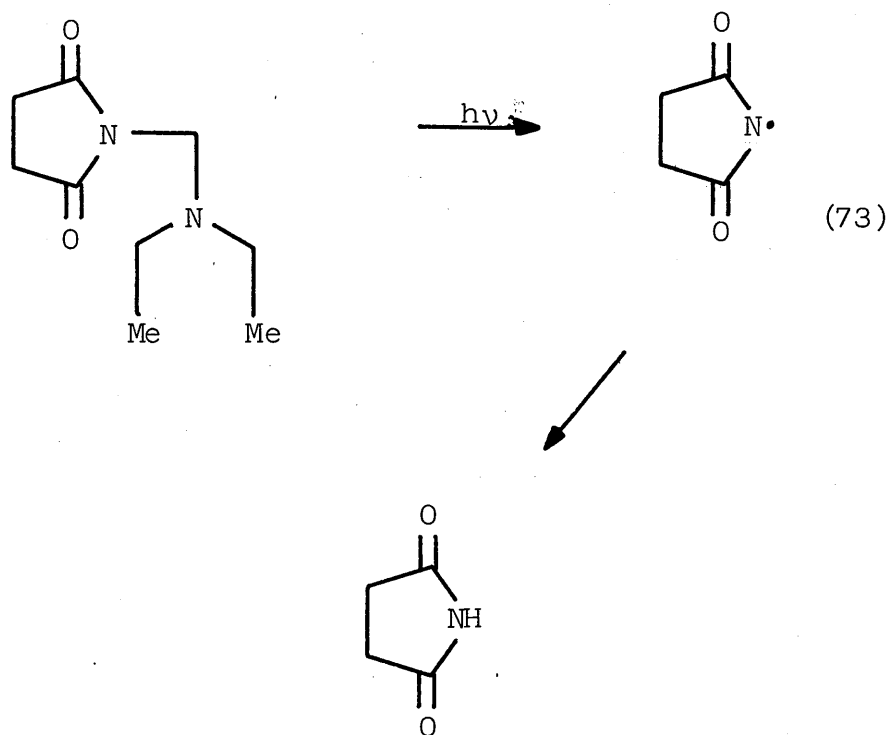
We attempted to determine the stereochemistry of the diastereoisomers by using pyridine-induced solvent chemical shifts in the ^1H -nmr⁹³. The experiment involved measuring the change in the chemical shift value for the methine hydrogen atom, on going from pyridine- d_5 to chloroform- d as solvent. Because of the ability of aromatic systems like pyridine to coordinate at electron-deficient sites within a solute molecule, protons situated in the vicinity of a polar functional group invariably experience a screening effect, as a result of the large anisotropy in the magnetic susceptibility of the aromatic system.⁹⁴ Hence, in pyridine- d_5 the hydrogen cis to the adjacent hydroxyl group should shift further from its position in chloroform- d than the hydrogen trans to the hydroxyl group. In practice, we found that virtually all the signals in both diastereoisomers of (65 f) shifted to the same extent, indicating that the pyridine had coordinated to other sites in the molecule.

The cyclised photoproducts could, in principle, be formed via the biradical produced by δ -hydrogen abstraction:



However, there is evidence in the phthalimide series⁹⁵ that electron-transfer plays a part in the mechanism.

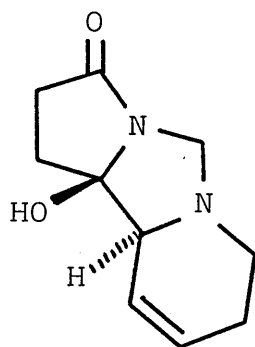
In virtually all these irradiations, the photocyclised products are the major photoproducts, but in some cases the parent (unsubstituted) imide was also produced. Irradiation of N-(diallylaminomethyl)succinimide gave 46% of (65 c) and 18% succinimide, and N-(morpholin-4-ylmethyl)glutarimide gave 12% impure (66 a) and 53% glutarimide. The irradiation of N-(diethylaminomethyl)succinimide gave succinimide (~100%) as the major photoproduct with only a very low yield of the cyclised products (65 d, 7%). The succinimide could be produced by a direct β -cleavage reaction in the excited state leading first to the succinimidyl radical (73).



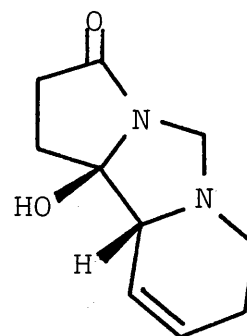
The yields of the cyclised photoproducts isolated from the irradiation of the succinimide Mannich bases were much higher (7, 46 - 77%), than those from the corresponding glutarimide substrates (12 - 36%). As already indicated the yields are based on unrecovered starting material, and we found that the quantity of starting material recovered from the irradiation of glutarimide Mannich bases is much lower than that recovered from the succinimide substrates. This suggests that for the glutarimides the formation of other products, which were not isolated by silica-gel column chromatography, competes effectively with the photocyclisation process.

Substrates from succinimideⁱ or glutarimide with formaldehyde and unsymmetrical secondary amines (1,2,5,6-tetrahydropyridine (62 e, 64 c and 64 g) or 1,2,3,4-tetrahydroisoquinoline (62 f, 64 b and 64 f)) could in principle lead to two pairs of products with different orientation.

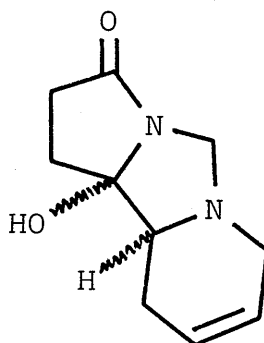
Irradiation of (62 e) gave three products in 56, 6 and 6% yields. The major product and one of the minor ones were assigned structures (74) and (75) corresponding to cyclisation to the activated allylic methylene group. The third product was assigned structure (76) corresponding to cyclisation at the non-allylic methylene group.



(74)



(75)



(76)

All the spectral data for the three products are similar, except for the positions of the alkene signals in the ^{13}C -nmr and ^1H -nmr spectra, and the doublets for cyclic NCH_2N in the ^1H -nmr. In (74) and (75) the alkene signals are at 130.2 and 120.7 ppm for one diastereoisomer and 128.2 and 122.2 ppm for the other in the ^{13}C -nmr spectra, indicating that the alkene carbon atoms are non-equivalent. (76) gave only a single signal at 124.5 ppm indicating that the alkene carbon atoms are still (almost) equivalent as in the Mannich base. The ^1H -nmr of (74) and (75) shows the alkene

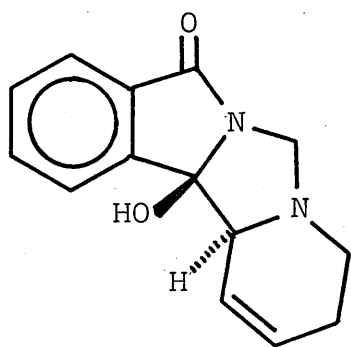
hydrogen atoms to be non-equivalent - the ranges covered by the multiplet signals are ~ 0.4 and 0.45 ppm. The multiplet for the alkene hydrogen atoms in (76) covers a range of only 0.06 ppm.

The signals for the hydrogen atoms of the NCH_2N group show a similar effect (but to a smaller extent) to that observed for the isomers of (65 a, b, and c). The difference in chemical shift for the NCH_2N hydrogen atoms for the structures (74 and 75) is 0.37 and 0.11 ppm respectively, compared with ~ 0.45 and ~ 1.15 ppm for the corresponding hydrogen atoms in (65 a, b and c). The third photoproduct was assigned structure (76), and the difference in chemical shift for the hydrogen atoms of the NCH_2N group in this compound is 1.24 ppm. This value is typical for the trans isomers of other photoproducts (e.g. 65 b) where our hypothesis is that the lone pairs of electrons on the nitrogen atoms are syn with respect to each other in a fairly rigid structure. The ^{13}C -nmr data for this product are consistent with its being the trans isomer, but this cannot be confirmed because the other isomer was not isolated.

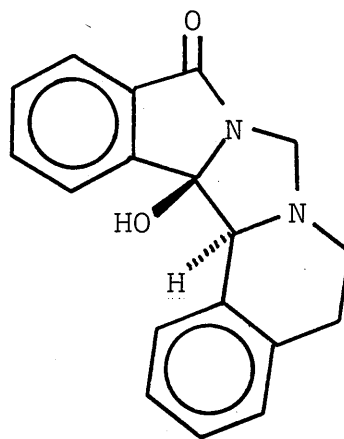
The ^1H - and ^{13}C -nmr spectral data for the structures (74 and 75) allow the stereochemistry to be assigned. The isomer with the bridgehead OH and H groups cis with respect to each other has the lower chemical shift value for the quaternary carbon (C-OH) and for the amide carbonyl carbon atom, and has a smaller coupling constant for the geminal hydrogen atoms of

the NCH_2N group; this is based on the ideas discussed previously (page 51). However, it is not clear why a smaller difference in chemical shift value for the hydrogen atoms of the NCH_2N group is observed for photoproducts derived from cyclic unsaturated or aromatic amines (i.e. with a $\text{C}=\text{C}$ multiple bond adjacent to the methine group). If the lone pairs of electrons on the nitrogen atoms are the major source of the shielding effect on one particular hydrogen atom of the NCH_2N group in all the photoproducts, we have to assume that for the photoproducts (65 e) and (65 f) part of this shielding effect on the hydrogen atom at higher field is lost without being transferred to the other hydrogen. We suggest, that for photoproducts with cyclic unsaturated or aromatic groups adjacent to the methine carbon, the conformation of the molecules is such that the hydrogen that is syn with respect to the lone pairs is moved slightly out of plane and hence experiences a smaller shielding effect.

Smaller chemical shift differences in the ^1H -nmr spectra for the hydrogen atoms of the NCH_2N group have been observed for the analogous phthalimide photoproducts (77) and (78). Only one stereoisomer of these photoproducts was obtained and the chemical shift difference in both cases was 0.3 ppm, which is consistent with our observed differences.



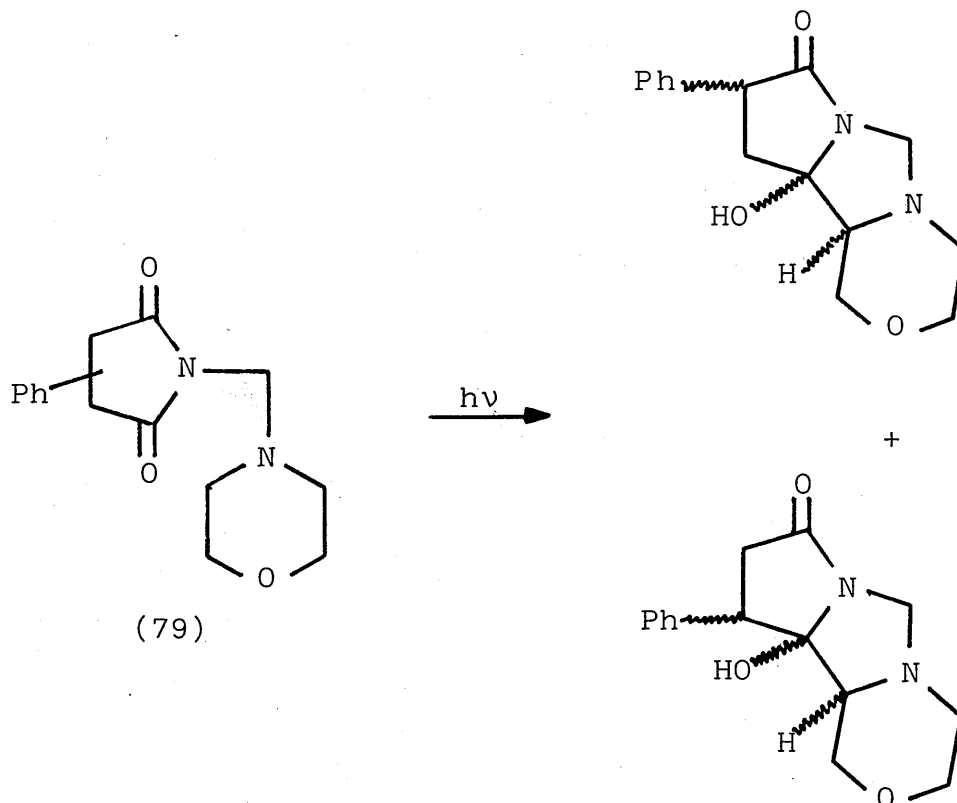
(77)



(78)

Of the examples where unsaturated substrates derived from unsymmetrical amines have been irradiated, only in the case of (65 e) has a third photoproduct been isolated where cyclisation has occurred at a position that is not between the amine nitrogen atom and the unsaturated group.

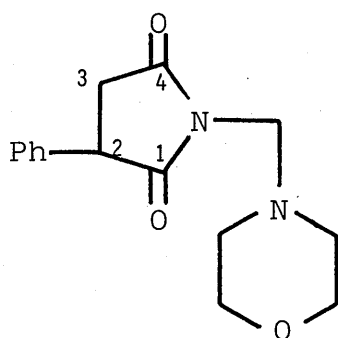
Having established a preference for attack at an activated methylene group in the amine part of the molecule, we were interested in determining if there was a preference for cyclisation to occur at a particular carbonyl group in substrates with an unsymmetrical imide ring. Substrates from unsymmetrical imides can in principle give diastereoisomeric photoproducts from two orientations of cyclisation. Hence, irradiation of N-(morpholin-4-yl-methyl)- 2-phenylsuccinimide (79) can give rise to eight possible cyclised photoproducts.



We found that this substrate gave a number of photo-products, and six were distinguished by T.L.C. What appeared to be the major photoproduct was isolated as a single component. The spectral data for this product indicated that it was a cyclised compound with the new imidazolidine ring. The product was assigned this structure on the basis of signals in the ^{13}C -nmr for a single carbonyl at 176.7 ppm and a quaternary carbon (C-OH) at 99.0 ppm, a pair of doublets in the ^1H -nmr at 4.78 and 3.68 ppm for the cyclic NCH_2N , and peaks corresponding to $(\text{M}^+ - \text{H}_2\text{O})$ and an ion $(\text{C}_5\text{H}_9\text{NO})$ corresponding to the base peak in the mass spectrum.

We had hoped that from the ^{13}C -nmr spectra we would be able to distinguish between the two possible orientations of cyclisation. The ^{13}C -nmr spectrum of (79) shows two carbonyl signals at 178.6 ($\text{O}=\text{C}-\text{CHPh}$) and

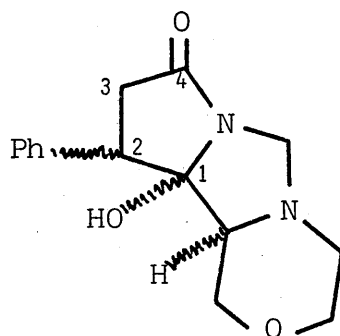
176.9 ppm ($\text{O}=\text{C}-\text{CH}_2$), and the methylene and methine carbon atoms of the succinimide ring at 36.9 and 46.0 ppm respectively.



1. 178.6
2. 46.0
3. 36.9
4. 176.9

(79)

The corresponding signals in the spectrum of the major photoproduct (80) can best be assigned on the basis of the structure:



1. 99.0
2. 48.0
3. 39.0
4. 176.7

(80)

The signal for the carbonyl, at 176.7 ppm, has virtually the same chemical shift value as the C-4 carbonyl of the Mannich base. However, the signals for the

methylene and methine carbon atoms (C-3 and C-2) do not contribute towards this assignment, and the structure must be regarded as tentative.

Two other isomers were isolated as components of mixtures which could not be further purified due to the small quantities involved and the similar polarity of these compounds.

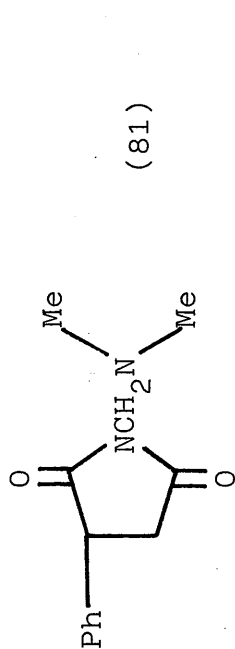
To investigate further the question of whether cyclisation occurs at both carbonyl groups in such a system, we irradiated the simpler derivative, N-(dimethylaminomethyl)-2-phenylsuccinimide (81) which should give a maximum of four cyclised photoproducts, two diastereoisomers from each orientation. In practice, four products were distinguished by T.L.C., and we isolated three of these isomers in workable quantities, and the fourth as a component of a mixture. The structure of the products was assigned on the basis of the information obtained from the ^{13}C -nmr and high-field ^1H -nmr spectra. This information, and the yields of each isomer are set out in the table below, along with the spectral data for the substrate (81).

The ^1H -nmr spectrum of the major photoproduct (82 a) shows a large upfield shift to 1.87 ppm for one of the doublets arising from a hydrogen atom on the CH_2N group adjacent to the quaternary (C-OH) carbon.

(81)

¹H-nmr

7.35 - 7.20	m, 5H
4.45	s, 2H
4.05	dd, J=9 and 5 Hz, 1H
3.25	dd, 18½ and 9 Hz, 1H
2.84	dd, J=18½ and 5 Hz, 1H
2.33	s, 6H



¹³C-nmr

178.6	61.2(t)
177.0	46.0(d)
137.3	43.1(intense, q)
129.3	37.1(t)
128.0	
127.3	

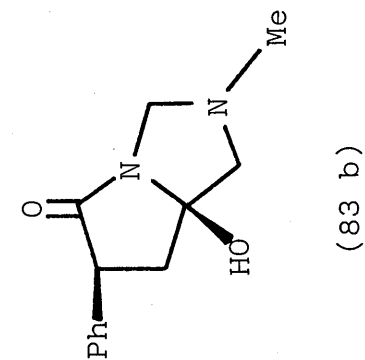
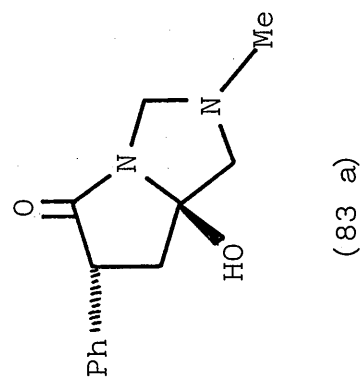
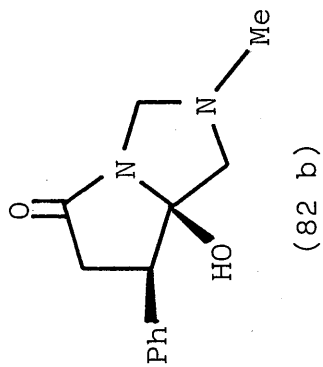
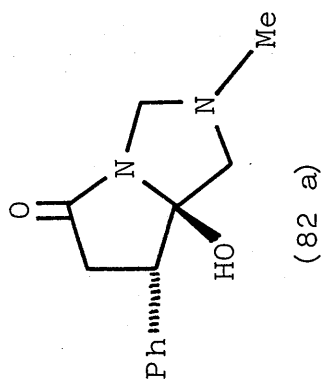


PLATE 4 (82 a)

¹H-nmr (0.32 g)

7.40 - 7.10	m, 5H
4.15	d, J=6 Hz, 1H
3.73	d, J=6 Hz, 1H
3.70	dd, J=8½ and 2½ Hz, 1H
3.44	dd, J=17 and 8½ Hz, 1H
2.62	dd, J=17 and 2½ Hz, 1H
2.55	d, J=9½ Hz, 1H
2.44	s, 3H
1.87	d, J=9½ Hz, 1H

¹³C-nmr

175.3	66.2(t)
139.7	62.4(t)
128.9	48.8(d)
127.5	39.8(q)
127.4	39.4(t)
99.0(s)	

PLATE 5 (82 b)

(0.14 g)

7.40 - 7.30	m, 5H
4.16	d, J=6½ Hz, 1H
3.89	d, J=6½ Hz, 1H
3.66	dd, J=12½ and 7½ Hz, 1H
3.30	dd, J=16 and 12½ Hz, 1H
3.01	d, J=9 Hz, 1H
2.83	d, J=9 Hz, 1H
2.63	dd, J=16 and 7½ Hz, 1H
2.42	s, 3H

175.1	95.9(s)
136.0	66.3(t)
128.9	66.1(t)
128.6	51.1(d)
128.4	39.5(q)
127.8	37.8(t)
126.3	

PLATE 6 (83 a)

¹H-nmr (0.05 g)

7.50 - 7.25	m, 5H
4.06	d, J=6½ Hz, 1H
3.95	d, J=6½ Hz, 1H
3.80	dd, J=10½ and 2½ Hz, 1H
3.01	d, J=9½ Hz, 1H
2.71	dd, J=14 and 10½ Hz, 1H
2.53	d, J=9½ Hz, 1H
2.39	dd, J=14 and 2½ Hz, 1H
2.40	s, 3H

¹³C-nmr

176.1	127.2	174.8	127.3
139.2	94.8(s)	137.4	92.9
130.9	66.4(t)	130.9	66.7
128.8	66.3(t)	130.7	66.3
128.4	51.5(d)	128.7	49.8
127.6	39.7(q)	128.4	39.5
	38.8(t)		37.8

PLATE 7 (83 b)

(0.03 g)

PLATE 4

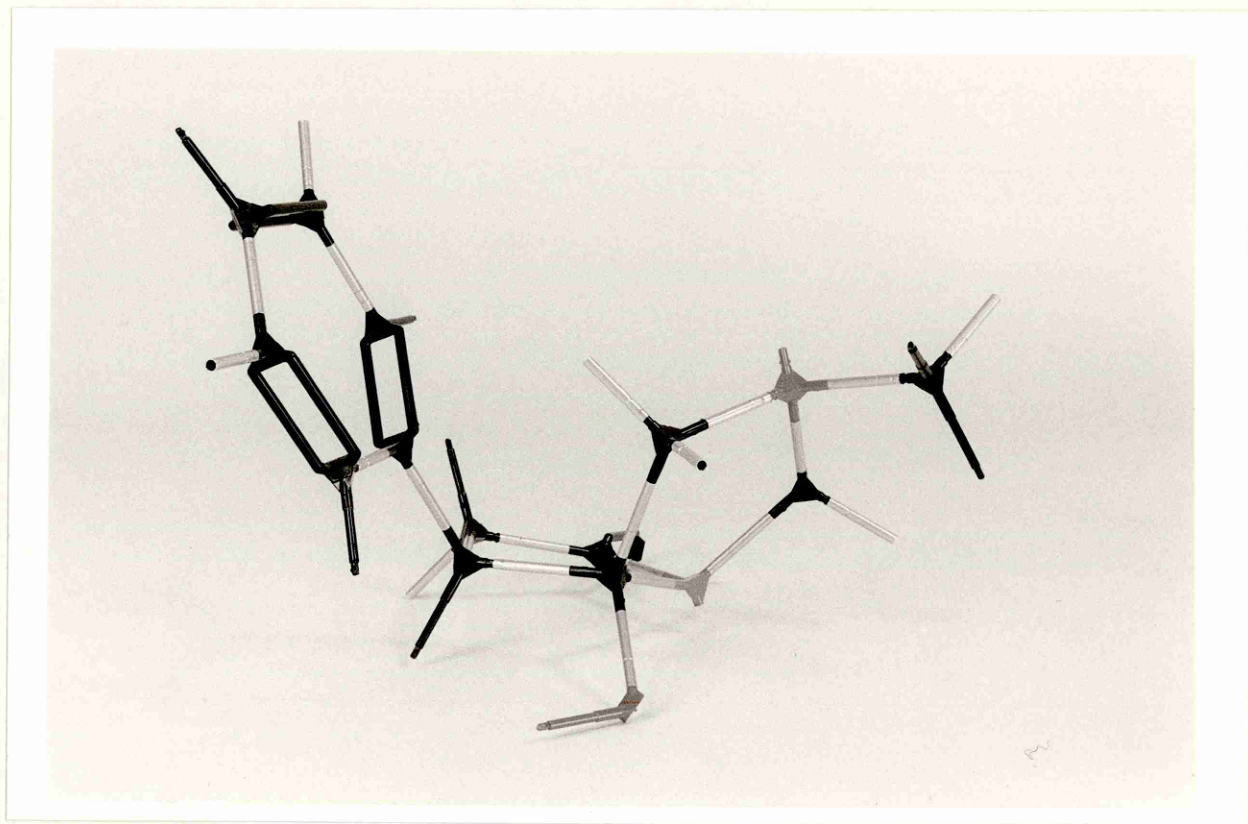


PLATE 5

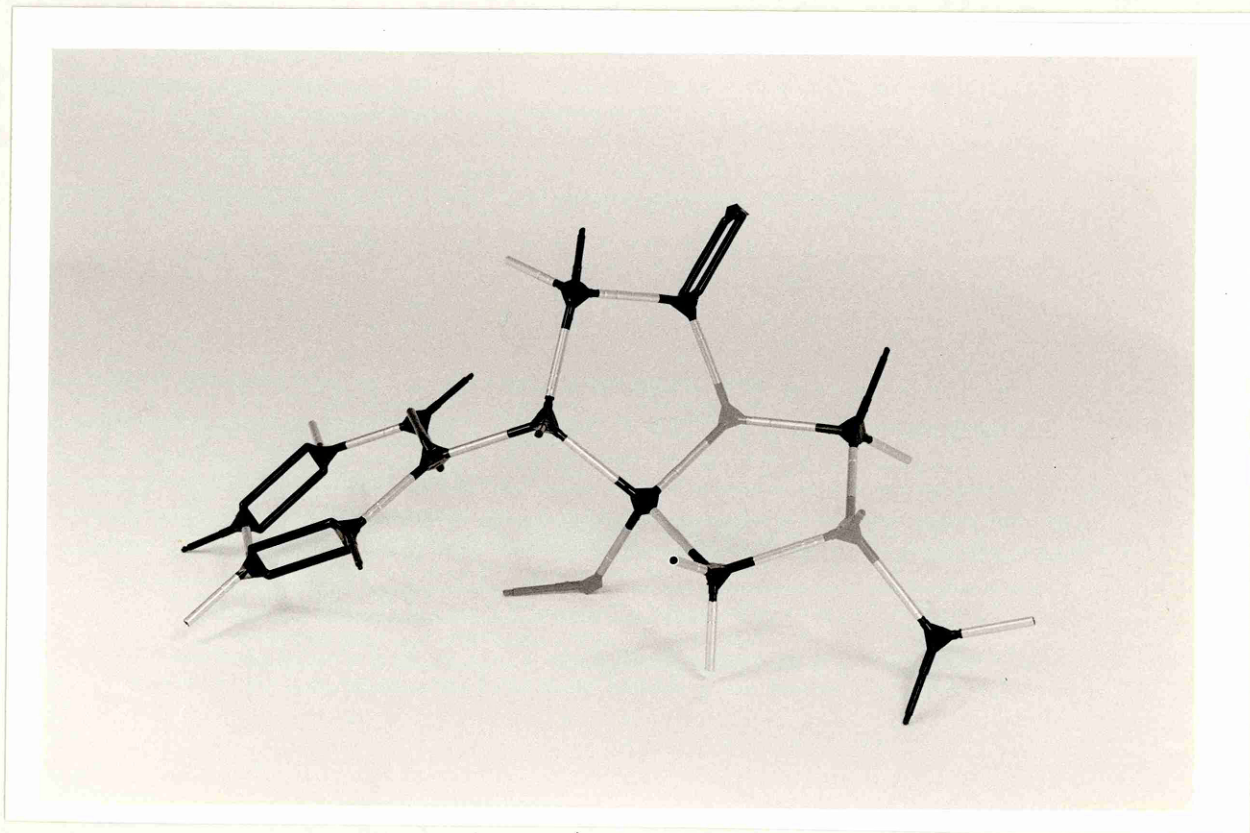


PLATE 6

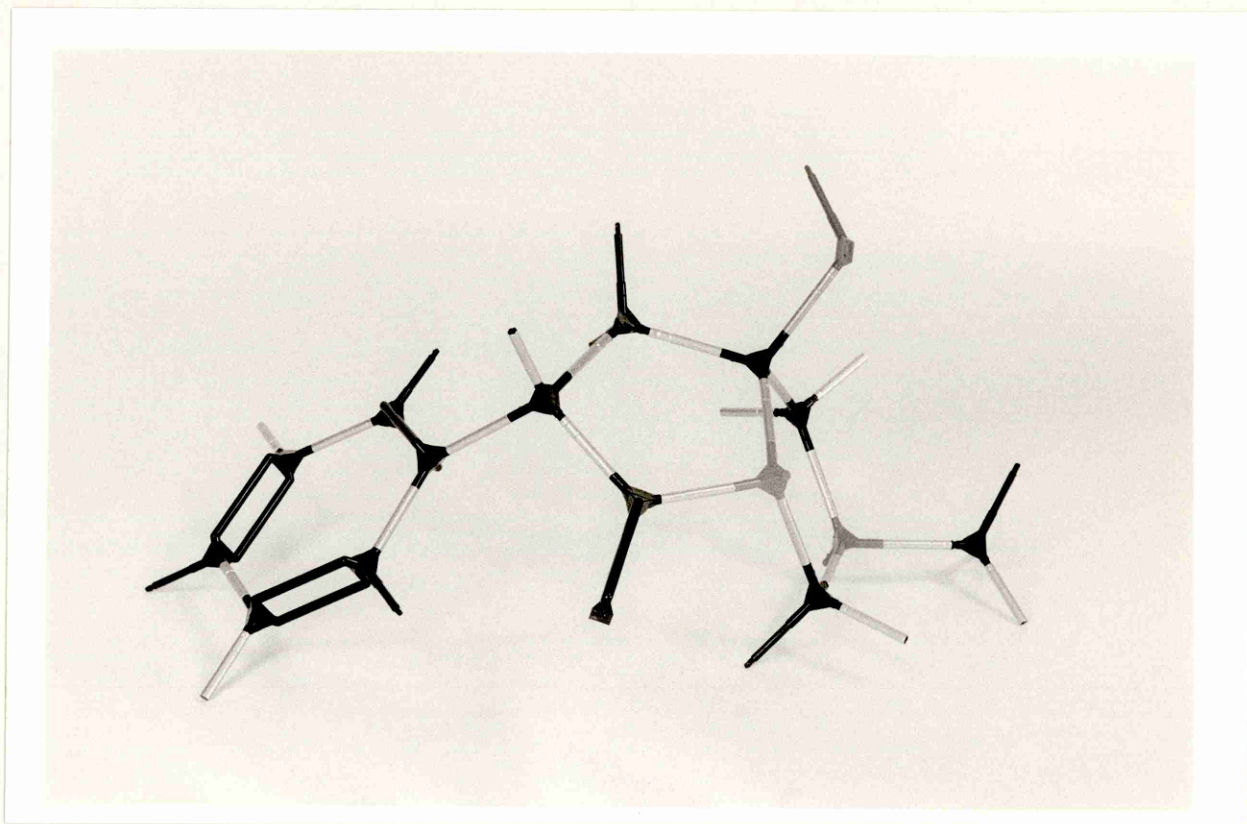
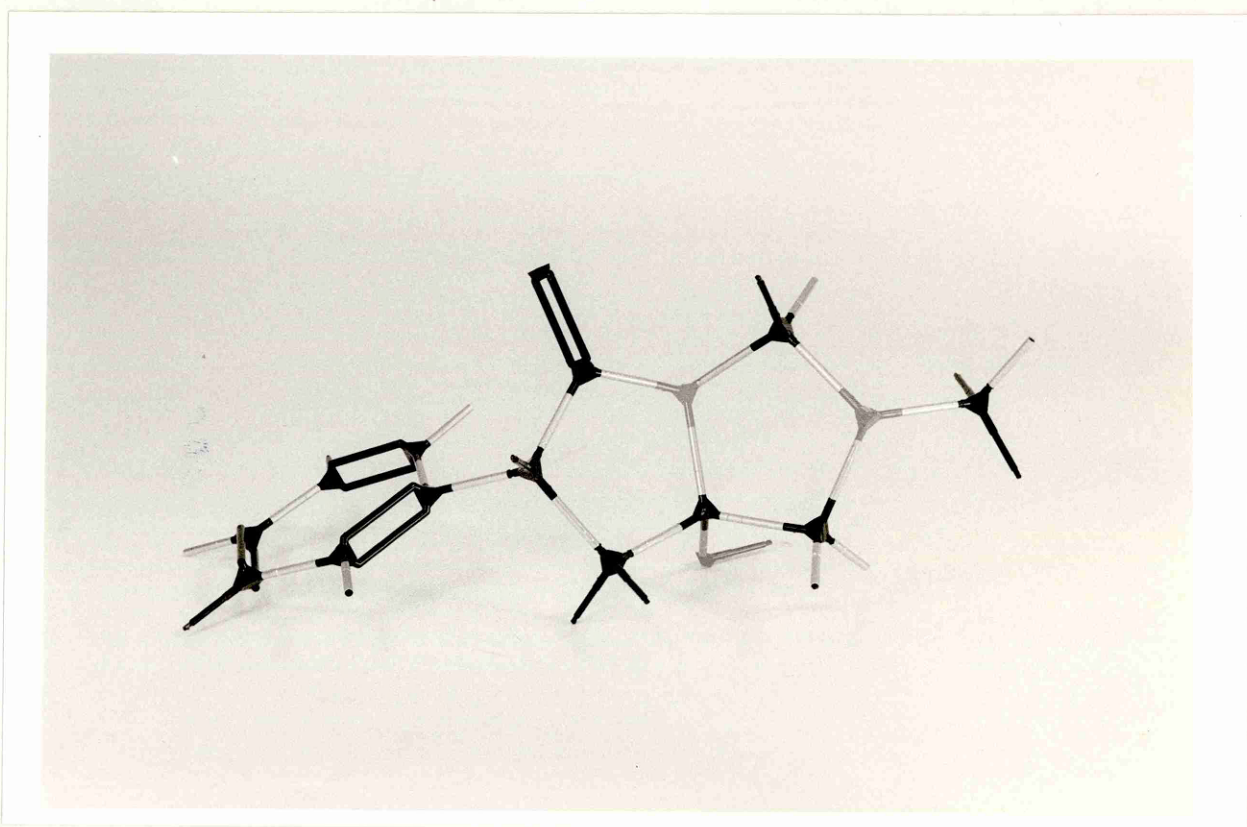


PLATE 7



We also observe in the ^{13}C -nmr spectrum that the chemical shift value of the signal assigned to the carbon atom of the CH_2N group adjacent to the quaternary carbon (C-OH) is lower (62.4 ppm) in isomer (82 a) than the typical value of 66 ppm for the remaining isomers (82 b, 83 a and 83 b).

This can only arise from a shielding effect by the phenyl ring, which gives a strong indication that the orientation of cyclisation, for this isomer (82 a), is to the carbonyl group adjacent to the CH-Ph group (plate 4). Cyclisation to the other carbonyl group (83 a and 83 b, plates 6 and 7) cannot give this effect. Molecular models of the diastereoisomers (82 a) and (82 b; plate 5) show that this effect of the phenyl ring can only occur in the isomer with the hydroxyl group and phenyl ring trans with respect to each other (82 a). The isomer with these groups cis (82 b) is less likely to give rise to this effect as it is not possible for the phenyl ring and the hydrogen atom to interact in the same way.

Although ^1H -nmr spectra for only three photoproducts were obtained, it is possible to compare the data and determine which corresponds to the second diastereoisomer of (82 a), i.e. the isomer with cyclisation at the C-1 carbonyl group, and with the OH/Ph groups cis. We have assigned the doublet of doublet signals with the highest chemical shift value to the hydrogen atom of the methine group, and the remaining doublets of doublets to the hydrogen atoms of the methylene

group adjacent to the CH-Ph group. The chemical shift values for two sets of the higher field signals (3.44 and 2.62 ppm, and 3.30 and 2.63 ppm) are very similar, and not too different from the substrate (81). We could, therefore, assume that these sets of results belong to two diastereoisomers with the same orientation of cyclisation, at the C-1 carbonyl group. The remaining higher field doublet of doublet signals are very different (2.71 and 2.39 ppm) from the signals of (82 a) and (82 b), and are shifted upfield from the signals in the substrate (81). Hence, for this isomer, cyclisation has occurred at the C-4 carbonyl group. As the ^1H -nmr data for (83 b) were so complex due to the isomer being a component of a mixture, we are unable to compare the data for (83 a) and (83 b), and so cannot confirm that we have assigned the correct orientation of cyclisation.

We can attempt to determine the stereochemistry of (83 a) by comparing the coupling constants of the signals for the hydrogen atoms at C-2 and C-3. Isomer (82 a) has been designated trans OH/Ph stereochemistry with cyclisation at the C-1 carbonyl group, and the similarity of the coupling constants for isomers (82 a) and (83 a) could indicate that isomer (83 a) has the same stereochemistry, with cyclisation at the C-4 carbonyl group.

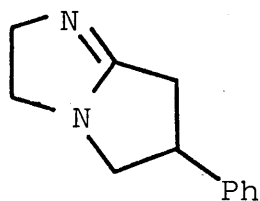
In the earlier part of this chapter, we suggested a possible reason why there was a large chemical shift difference between the signals in the ^1H -nmr spectra

for the hydrogen atoms of the NCH_2N group for the photoproducts (65 a, b and c). We have observed that for the isomers (82 a, b and 83 a) there is only a very small difference in the chemical shift value for these hydrogen atoms, and this is in keeping with our hypothesis that for a photoproduct derived from an N-(dimethylaminomethyl)succinimide substrate, rapid inversion of the amine nitrogen atom occurs and hence the degree of shielding of the higher field hydrogen atom is greatly decreased.

From these results, we conclude that cyclisation can occur at either carbonyl group in an unsymmetrical succinimide, although, from the ratio of the isomers, the preferred orientation of cyclisation is at the C-1 carbonyl group (adjacent to the CH-Ph group) in the 2-phenylsuccinimide substrates. This could be due to an interaction of the δ -positive amine nitrogen atom arising from an initial electron transfer mechanism, with the electrons of the aromatic ring, which allows transfer of a proton to the C-1 carbonyl rather than C-4 (due to the proximity of the methyl group to C-1). The major diastereoisomer (82 a) is the most sterically hindered, and we believe that ring closure is very rapid after the transfer of a proton has taken place, and this preserves the cis stereochemistry between the phenyl ring and the methylene group ($\text{NCH}_2\text{C-OH}$) forcing the hydroxyl group trans. Greater selectivity might be expected if one of the methylene groups of succinimide is replaced by a heteroatom and accordingly we studied the photochemical cyclisation of Mannich bases derived from hydantoins. These results are described

in chapter 3.

The photochemical cyclisation of the Mannich bases leads to polycyclic heterocyclic products with lactam and tertiary alcohol functional groups, and we wanted to investigate the possibility of thermal transformations of these photoproducts. Some related pharmacologically active compounds are less highly oxygenated, as in (84), which is an antihypertensive agent, so we attempted to remove the hydroxyl group from (65 f and 66b) and the carbonyl group from (65 f).



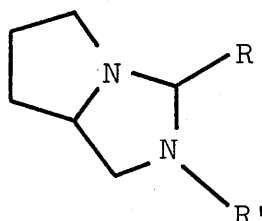
(84)

As previously discussed, mass spectra were obtained for many of the photoproducts, and in each case a small ion corresponding to the loss of water ($M^+ - H_2O$) was seen. These data encouraged us to be optimistic about the success of dehydration.

The major isomers of (65 f) and (66 b) were treated with acid or base under various conditions: reflux in aqueous hydrochloric acid, reflux with acetic anhydride/sodium acetate, or a room temperature reaction with concentrated hydrochloric acid in chloroform. In each case, dark-coloured gums were obtained which were found to be

complex mixtures. We also attempted to reduce the carbonyl group of (65 f) using different reducing agents such as borane - tetrahydrofuran complex, lithium aluminium hydride or diisobutylaluminium hydride, but again the reaction mixtures were found to contain many products.

Compounds similar to the fully reduced compounds we attempted to make from the photoproducts, have been prepared thermally, (e.g. 85).⁹⁶



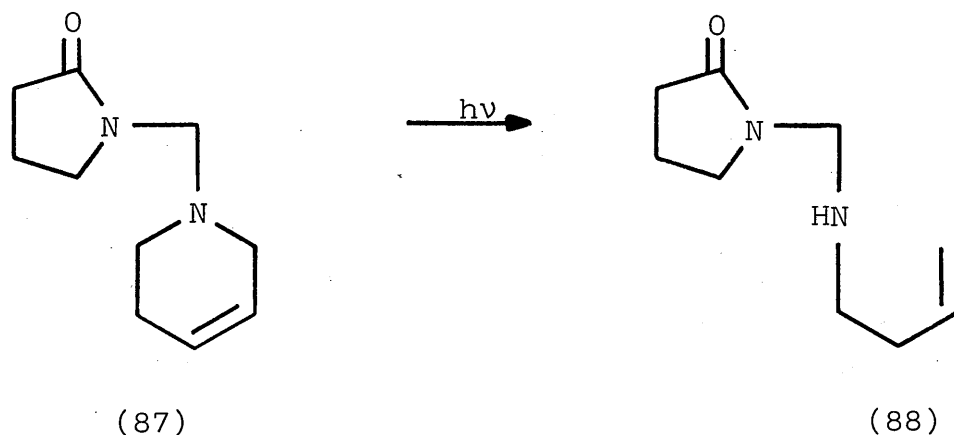
(85)

Pyrrolidin-2-one Mannich bases:

Imides behave like ketones in many of their photochemical reactions, but amides seem to be quite different, and little intramolecular photochemistry of saturated amides is synthetically useful.¹⁴ Mannich bases of the cyclic amide, pyrrolidin-2-one, have been prepared before,⁸² and we irradiated some of these substrates to investigate whether the amides undergo the same photochemical cyclisation reaction as the corresponding

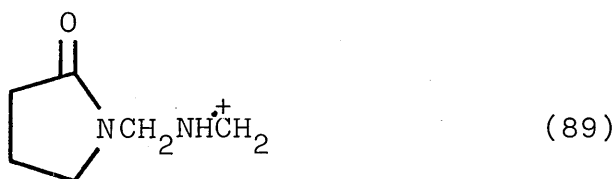
succinimides.

N-(Morpholin-4-ylmethyl)- and N-(1,2,5,6-tetrahydro-pyridin-1-ylmethyl)pyrrolidin-2-one (87) gave complex mixtures on irradiation. From the latter substrate (87) a small amount (6%) of a photoproduct was isolated and identified by spectral data as N-(but-3-enylamino-methyl)pyrrolidin-2-one (88).



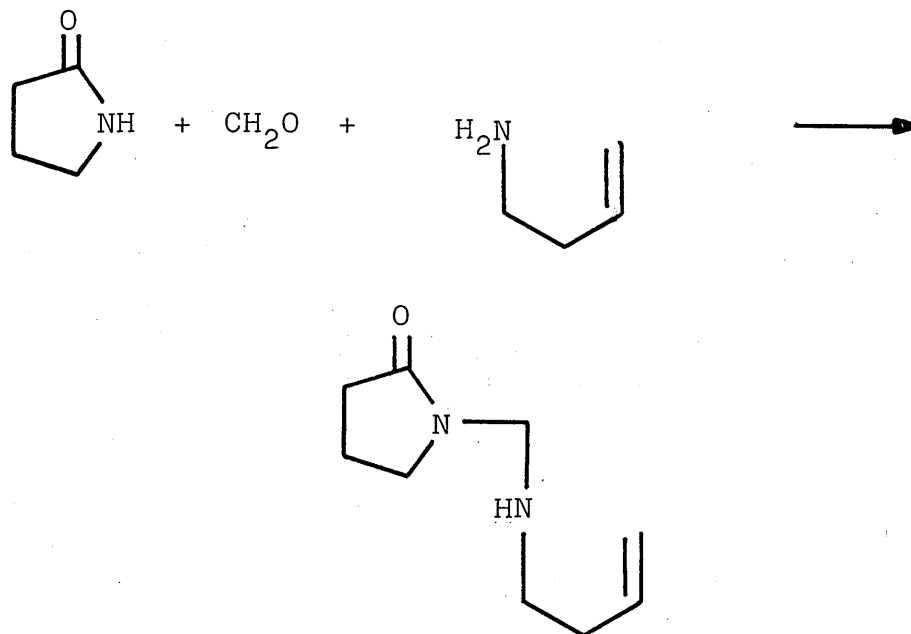
Our hypothesis that the photoproduct has this structure is based on the following spectral data. The ^{13}C -nmr spectrum shows nine signals. A singlet at 175.7 ppm and triplets at 46.6, 31.3 and 18.0 ppm are characteristic of an intact pyrrolidin-2-one ring (the corresponding signals for (87) appear at 175.6, 47 - 50, 31.1 and 18.0 ppm respectively). Two signals at 136.2 (doublet) and 116.5 (triplet) ppm indicate a vinyl group. There are three other triplets at 57.3, 45.6 and 34.1 ppm. The infrared spectrum shows weak bands at 3225 and 3110 cm^{-1} which are typical of a secondary amine NH

and alkene CH stretching modes, and a strong absorption band at 1685 cm^{-1} indicating the presence of a cyclic five-membered amide carbonyl group. A shoulder at 1640 cm^{-1} could suggest the presence of an alkene group. Signals in the ^1H -nmr spectrum at 6.15 - 5.50 (1H) and 5.30 - 4.80 ppm (2H) show the characteristic pattern for the alkene protons of an allylic group, $\text{CH}_2\text{CH}=\text{CH}_2$. The mass spectrum of (88) did not give a molecular ion (M^+), but the fragmentation pattern supplied information about the substituent on the amide nitrogen. An ion at $m/e = 127(\text{C}_6\text{H}_{11}\text{N}_2\text{O})$ corresponds to (89),

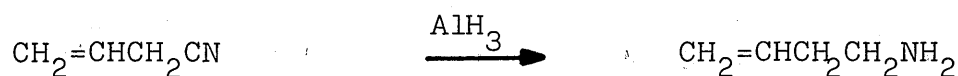


and ions at $m/e = 113(\text{C}_5\text{H}_9\text{N}_2\text{O})$, 98(base, $\text{C}_5\text{H}_8\text{NO}$) and 84($\text{C}_4\text{H}_6\text{NO}$) indicate the successive fragmentation of (89).

The formation of (88) represents a most unusual photochemical process, and so to confirm the structure, we attempted to synthesise the photoproduct by a thermal route, involving the reaction of pyrrolidin-2-one, formaldehyde and the primary amine, but-3-enylamine.

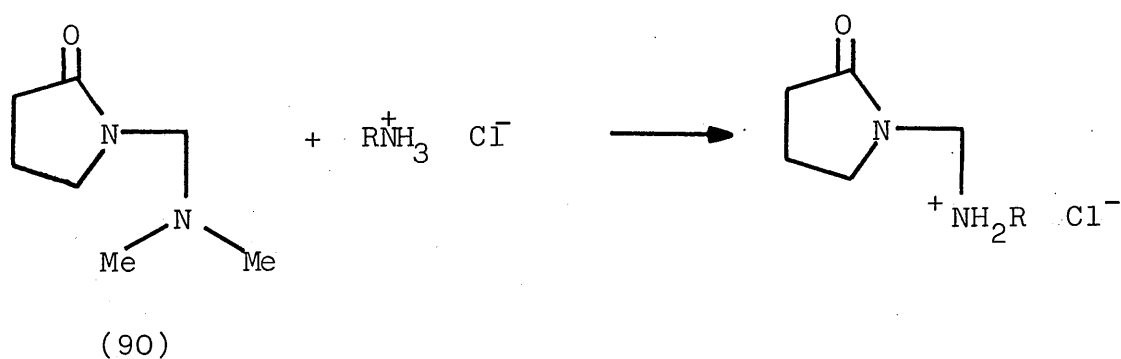


But-3-enylamine is not available commercially, and was prepared by the reduction of but-3-enenitrile with aluminium hydride.⁹⁷

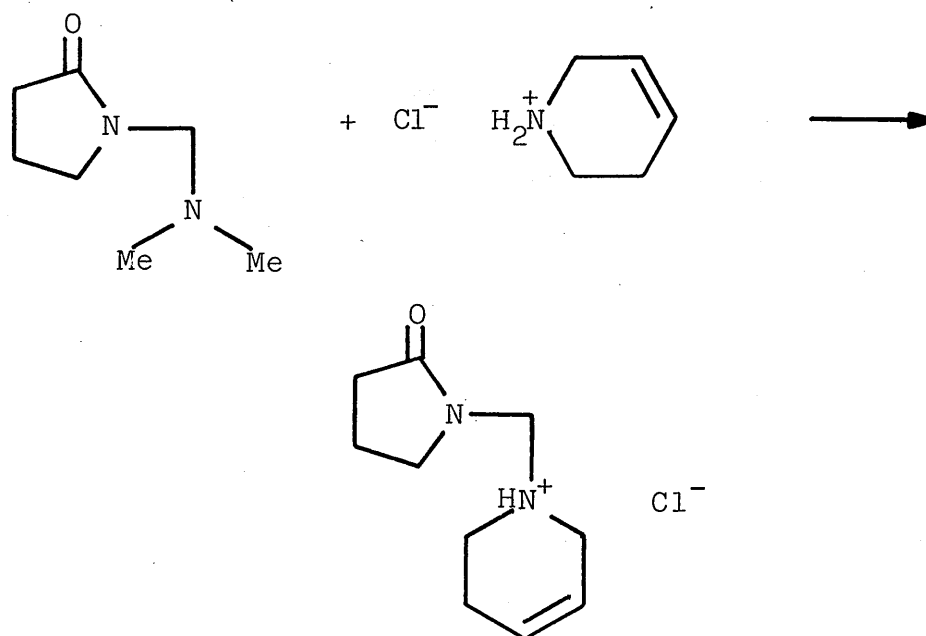


The yield of amine isolated as the hydrochloride salt, was low, and so the subsequent reactions were first tried using the readily available saturated analogue, butylamine.

Amine exchange reactions involving Mannich bases have been used before⁹⁸ and we attempted to carry out an exchange using a primary amine with the Mannich base N-(dimethylaminomethyl)pyrrolidin-2-one (90) derived from a secondary amine.

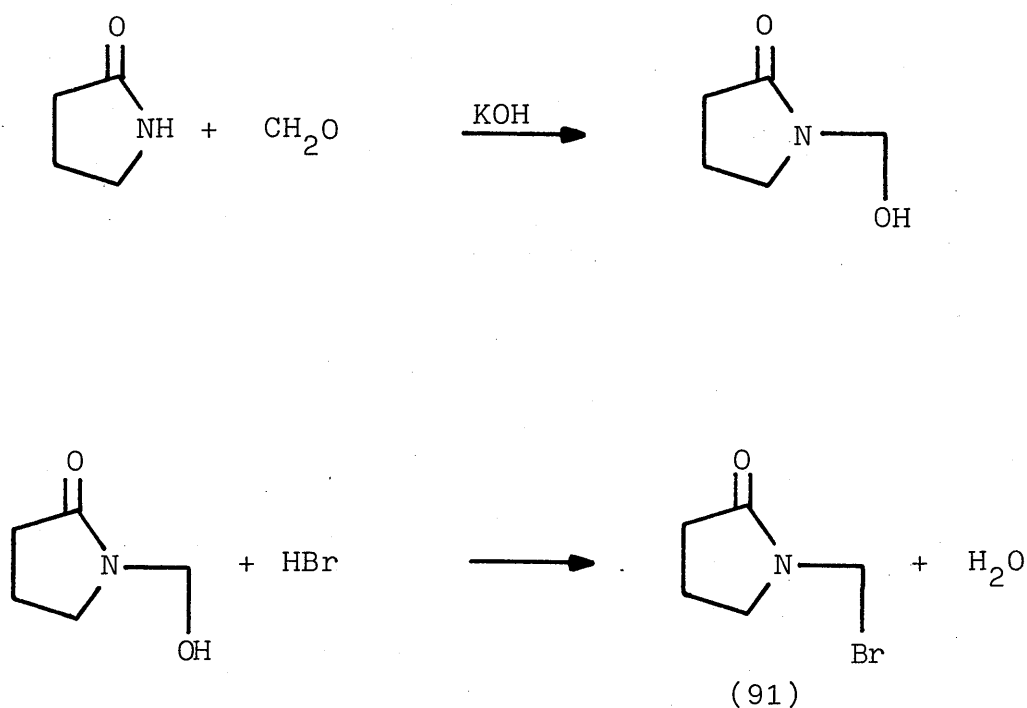


Heating (90) with butylammonium chloride gave a complex mixture, and a similar result was obtained when the reaction was repeated with but-3-enylammonium chloride. The reaction of the Mannich base (90) with 1,2,5,6-tetrahydropyridinium chloride gave a major product which was identical to the previously prepared N-(1,2,5,6-tetrahydropyridin-1-ylmethyl)pyrrolidin-2-one (87).

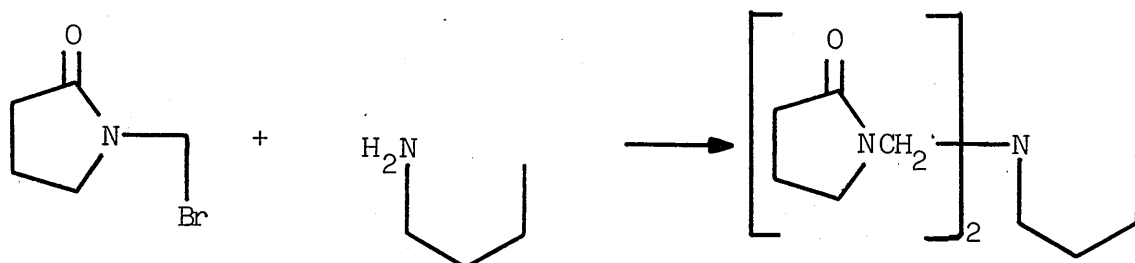


The results of these investigations lead us to the conclusion that the exchange reaction works with secondary amines but not with primary amines.

As an alternative approach, we prepared N-(bromomethyl)-pyrrolidin-2-one (91) from pyrrolidin-2-one, by first treating with formaldehyde in the presence of a strong base, and then reacting the N-(hydroxymethyl)pyrrolidin-2-one with hydrogen bromide.

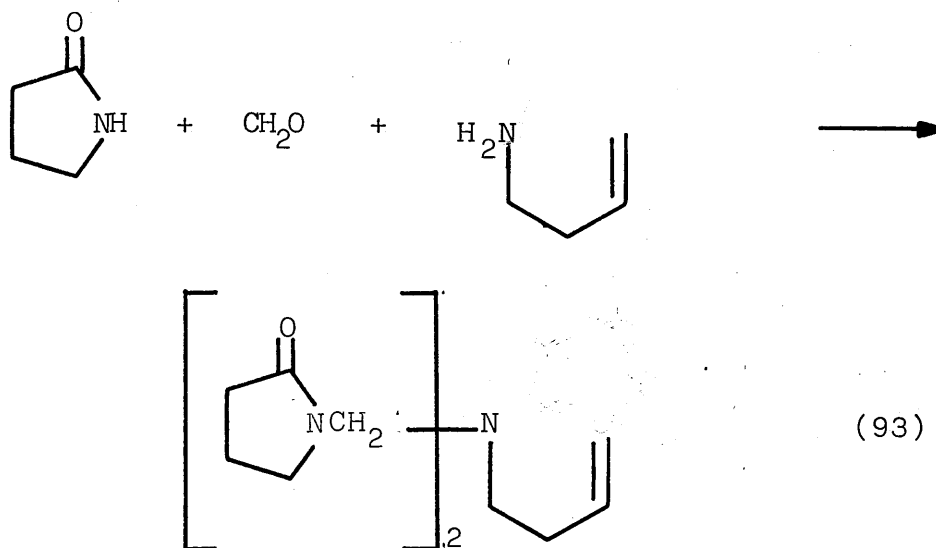


We then attempted to prepare a primary amine Mannich base from the reaction of (91) with a primary amine. However, butylamine gave a bis Mannich base (92) on reaction with N-(bromomethyl)pyrrolidin-2-one.



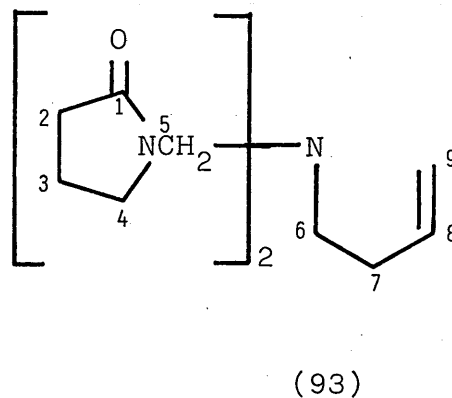
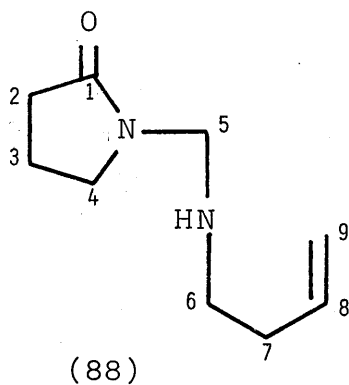
(92)

This product (92), and the corresponding bis Mannich base of but-3-enylamine (93) were isolated from the reaction of pyrrolidin-2-one, formaldehyde and the respective amine.



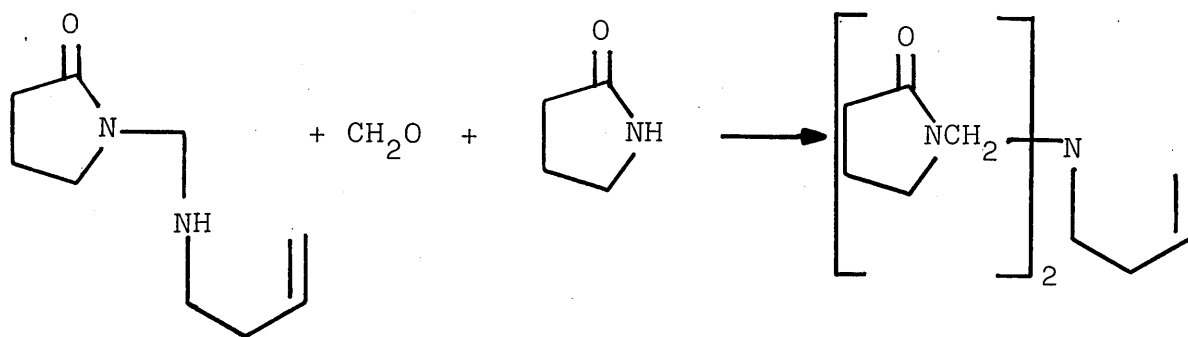
(93)

The ^{13}C -nmr and ^1H -nmr spectra of N,N-bis(2-oxopyrrolidin-1-ylmethyl)but-3-enylamine (93) and the photoproduct (88) are very similar, and documented below.



$^{13}\text{C-nmr } \delta / \text{ppm}$		
175.7	1	175.8
31.3	2	31.3(intense)
18.0	3	18.0(intense)
45.6/46.6	4	47.0(intense)
57.3	5	60.4(intense)
45.6/46.6	6	49.7
34.1	7	32.2
136.2	8	136.6
116.5	9	115.9
$^1\text{H-nmr } \delta / \text{ppm}$		
4.24 (s, 2H)	5	4.20 (s, 4H)
6.15 - 5.50 (m, 1H)	8	6.15 - 5.45 (m, 1H)
5.30 - 4.80 (m, 2H)	9	5.25 - 4.80(m, 2H)

From these reactions, it appears that mono Mannich bases cannot be prepared directly using primary aliphatic amines, and the photoproduct we isolated is the first of its type in the pyrrolidin-2-one series. For completion of the synthetic characterisation we treated the photoproduct with pyrrolidin-2-one and formaldehyde.



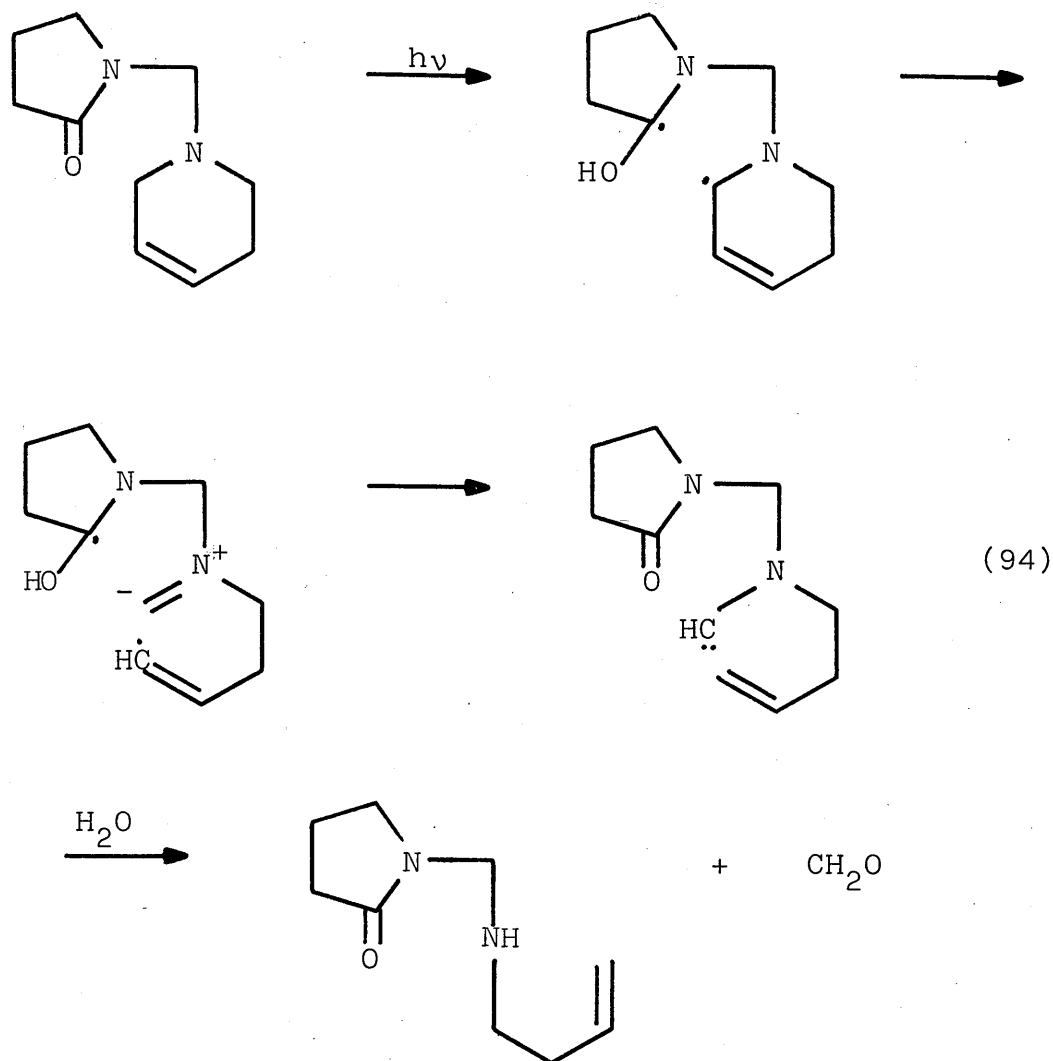
The reaction involved very small quantities of reactants and the major product could not be isolated, but it did have the same R_f value as (93) on T.L.C. analysis.

From the results of irradiating Mannich bases derived from pyrrolidin-2-one, we can conclude that the amide substrates do not behave in the same way photochemically as the imide substrates, although it should be realised that most of the photolysed substrate is not accounted for. The photoproduct isolated from the irradiation of N-(1,2,5,6-tetrahydropyridin-1-ylmethyl)pyrrolidin-2-one is very unusual with the overall process being the loss of just a carbon atom. Although we do not fully understand the mechanism of this process, a plausible approach can be put forward.

The loss of carbon has to involve the breaking of two bonds, a carbon-carbon bond and a carbon-nitrogen bond. The most straightforward process would involve loss of the activated methylene group at C-10.

A possible sequence (94) involves transfer of a hydrogen atom from C-10 to the excited amide carbonyl group, followed by carbon-carbon cleavage in the biradical so formed, reverse hydrogen transfer from the hydroxyalkyl radical, and eventual loss of the single carbon atom

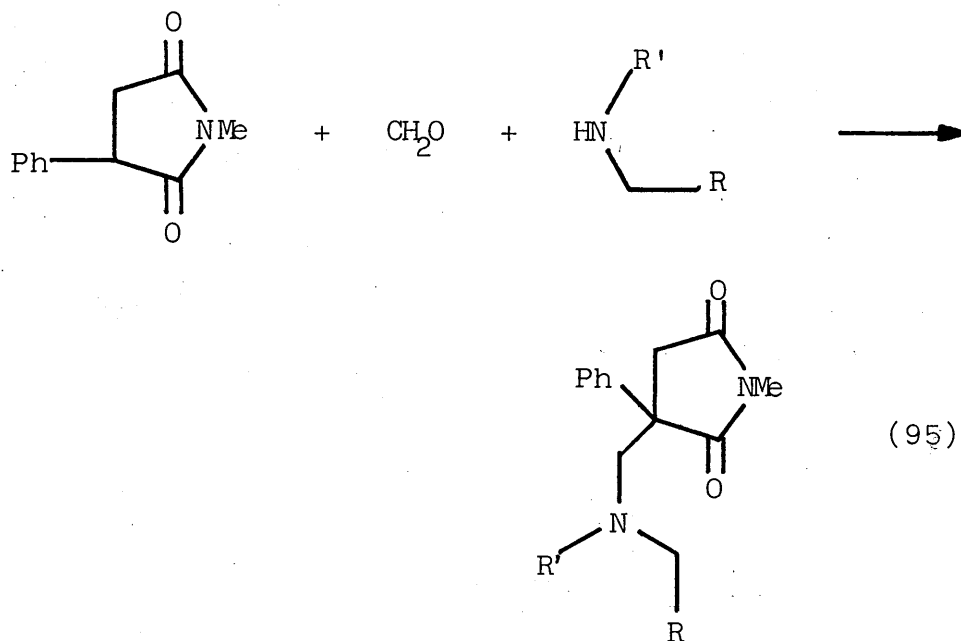
as formaldehyde.



2-Phenylsuccinimide Mannich bases

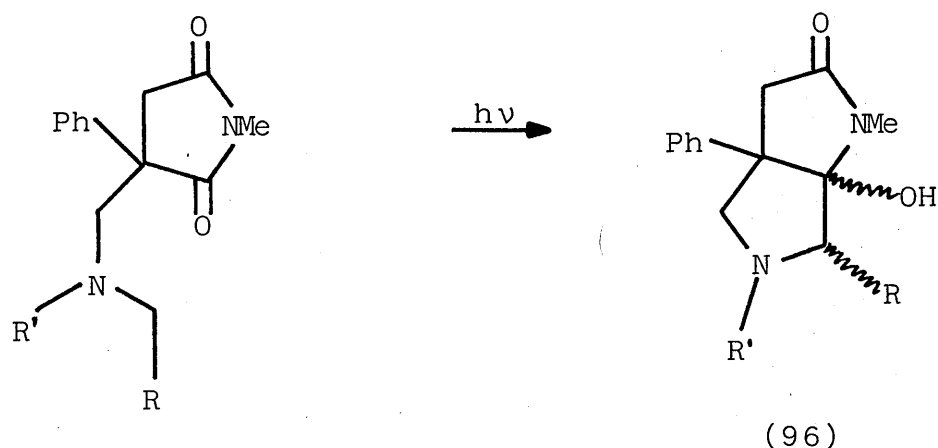
The Mannich reaction takes place between formaldehyde, an amine and a compound with a labile hydrogen atom. So far in this chapter, the 'active hydrogen' compound has been an imide with the labile hydrogen on the nitrogen atom. If the nitrogen of succinimide is blocked using an alkyl group, the Mannich reaction can occur at a CH position adjacent to the carbonyl instead of at NH, especially if this position is further activated

by an aryl group.^{77, 79} N-Methyl-2-phenylsuccinimide is such a substrate and we made Mannich bases from this imide (95).



- (a) $R, R' = (CH_2)_4$
- (b) $R, R' = CH_2OCH_2CH_2$
- (c) $R, R' = CH=CHCH_2CH_2$
- (d) $R = CH_3; R' = CH_2CH_3$

Mannich bases of this type have previously been prepared^{77 - 80}, and intensively studied for their anticonvulsant activity. Our interest involved their photochemical reactivity and possible photocyclisation. This could lead to polycyclic heterocyclic ring systems, and the products would be 2,7-diazabicyclo[3.3.0]octanes.



However, we found that on irradiation all the substrates gave complex mixtures. In the case of N-methyl-2-phenyl-2-(piperidin-1-ylmethyl)succinimide (95 a) a small quantity (5%) of a photoproduct was isolated, whose spectral data indicated that photocyclisation may have occurred. The infrared spectrum of the product showed a single carbonyl band at 1670 cm^{-1} , and a broad band at 3320 cm^{-1} indicative of a hydroxyl group. The ^1H -nmr spectrum also indicated that reaction had occurred at a carbonyl group since there was an upfield shift from 3.01 to 2.89 ppm for the methyl group attached to the nitrogen atom. These results are consistent with structure (96 a; R, R = $(\text{CH}_2)_4$), although they are far from conclusive.

Higher homologues of Mannich bases

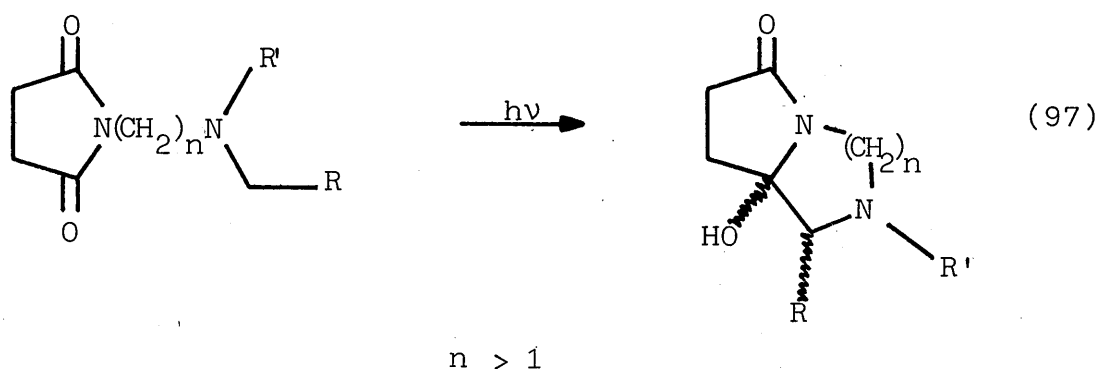
It has been reported previously⁴⁷ that irradiation

of N-(dialkylaminoalkyl)phthalimides (36) and (39) gives photocyclised products with a new ring containing more than five atoms.

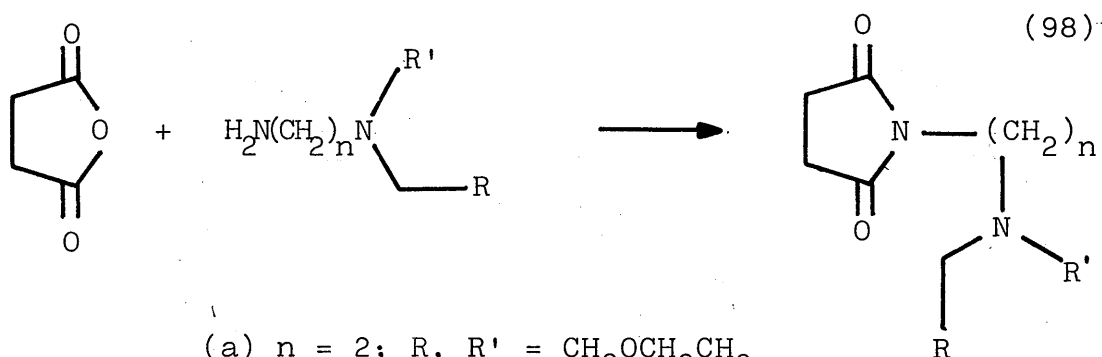
The corresponding (methylthioalkyl) analogues also give photocyclised products with larger rings (40)⁴⁸,
49.

A study⁵⁷ of the (methylthioalkyl) derivatives of succinimide has shown that these substrates form low yields of products by way of γ -hydrogen abstraction, leading to seven-membered lactams. (44 and 45).

These results led us to investigate the photoreactions of (dialkylaminoalkyl)succinimides with the possibility of preparing photocyclised products with larger rings (97) than the imidazolidine derivatives obtained from Mannich bases.



The (2-dialkylaminoethyl)- and (3-dialkylaminopropyl)- substrates were prepared by the reaction of succinic anhydride with a (dialkylaminoalkyl)amine (98), or glutarimide (99) or 1,2,3,6-tetrahydrophthalimide (100) with a dialkyl(chloroalkyl)amine.

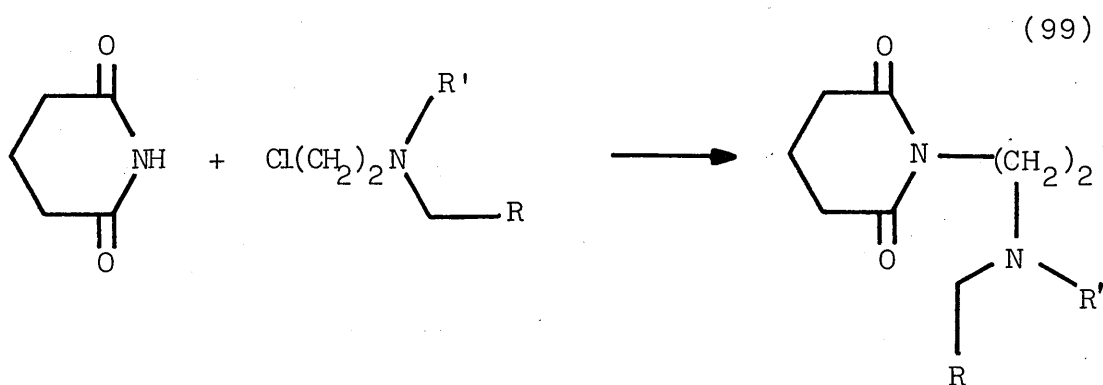


(a) $n = 2$; $R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$

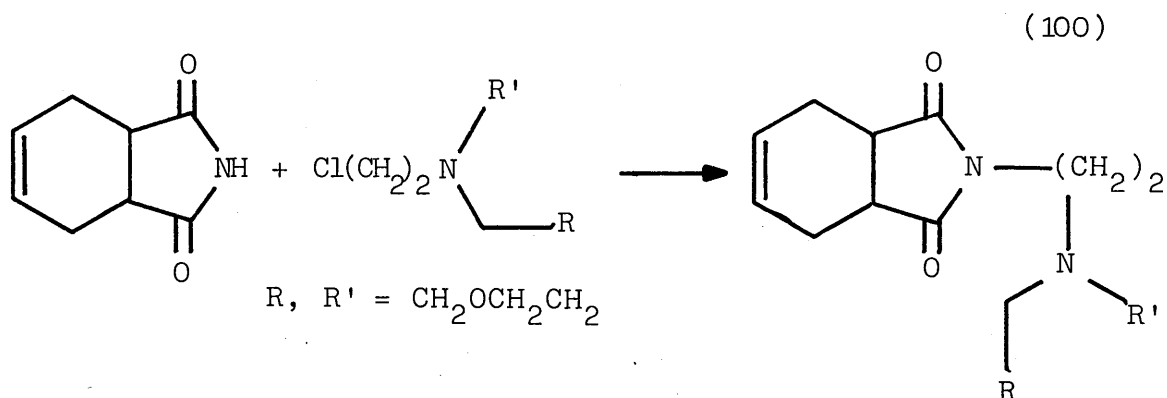
(b) $n = 2$; $R = \text{H}$; $R' = \text{CH}_3$

(c) $n = 3$; $R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$

(d) $n = 3$; $R = \text{H}$; $R' = \text{CH}_3$

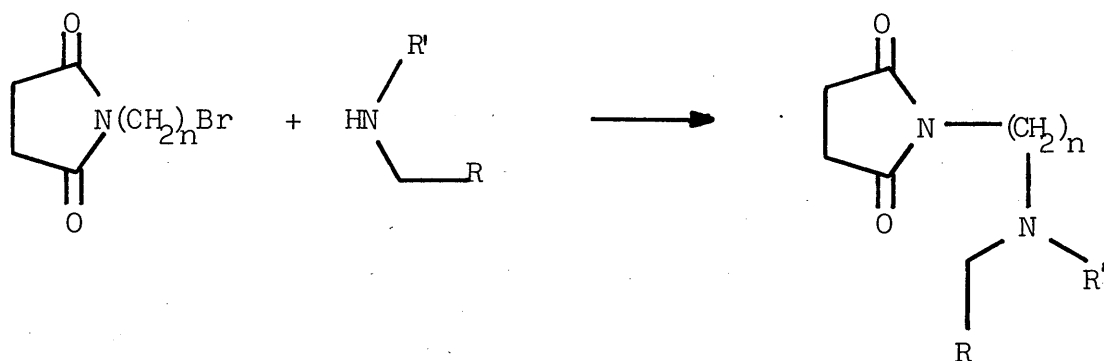
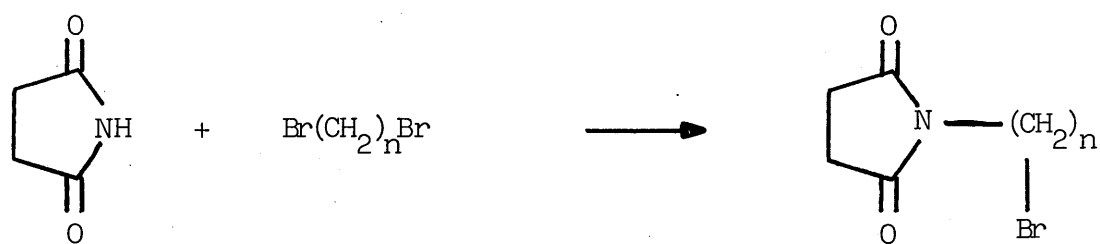


$R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$



$R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$

The (4-dialkylaminobutyl)- and higher homologues were prepared by a two-stage sequence from succinimide and the appropriate dibromoalkane in excess, followed by treatment of the (bromoalkyl)succinimide with a secondary amine (101).



(101)

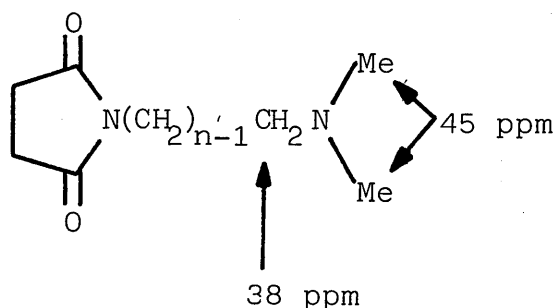
(a) $n = 4$; $\text{R}, \text{R}' = \text{CH}_2\text{OCH}_2\text{CH}_2$

(b) $n = 4$; $\text{R} = \text{H}$; $\text{R}' = \text{CH}_3$

(c) $n = 5$; $R = H$; $R' = CH_3$

(d) $n = 6$; $R = H$; $R' = CH_3$

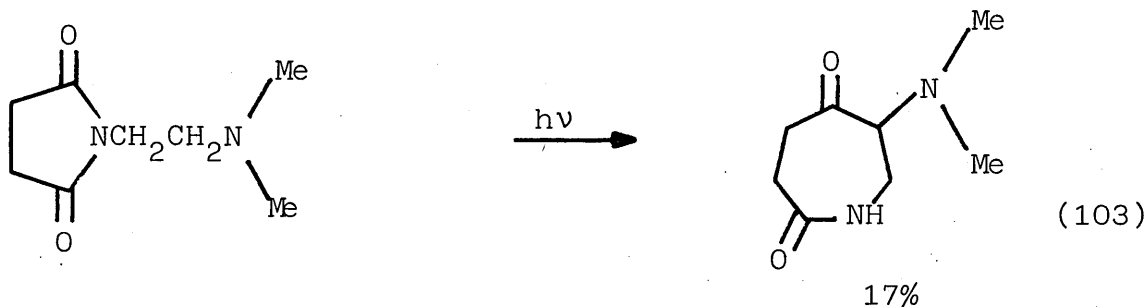
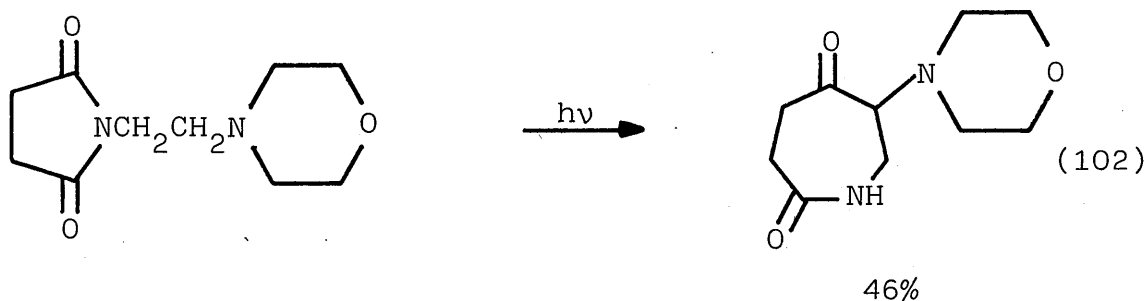
All the (dialkylaminoalkyl)- substrates were isolated either as hydrochloride salts, or by silica-gel column chromatography. Their characteristic spectral data are very similar to those of the Mannich bases, except for the absence of the low-field NCH_2N signals in the 1H -nmr and ^{13}C -nmr spectra and the presence of higher field signals for $N(CH_2)_nN$. The N-(dimethylaminoalkyl)- substrates exhibit some unusual chromatographic and spectroscopic behaviour. These compounds have exceptionally low R_f values on T.L.C. compared with the corresponding N-(morpholin-4-ylalkyl)- substrates. This made the mixtures after photolysis very difficult to handle especially for systems with $n > 3$, and in some cases no product could be isolated. In the ^{13}C -nmr spectra the N-methyl signals are at much higher chemical shift value than the methylene group attached to the same nitrogen atom, which is not expected simply on the basis of the deshielding effect of the nitrogen atom.

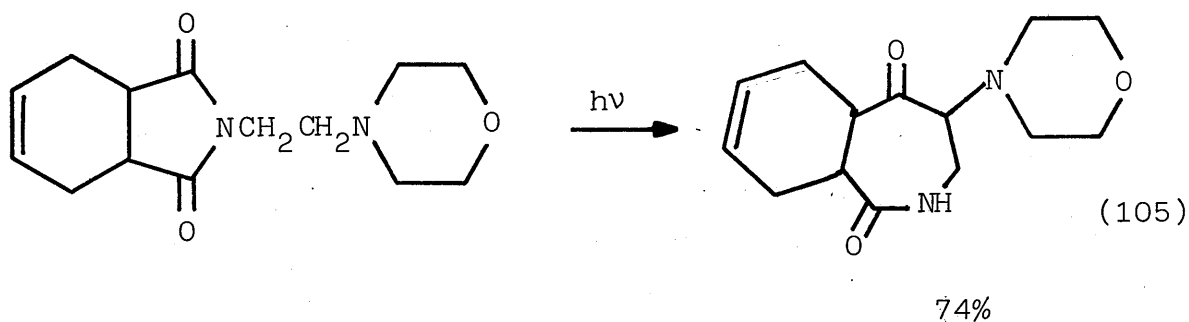
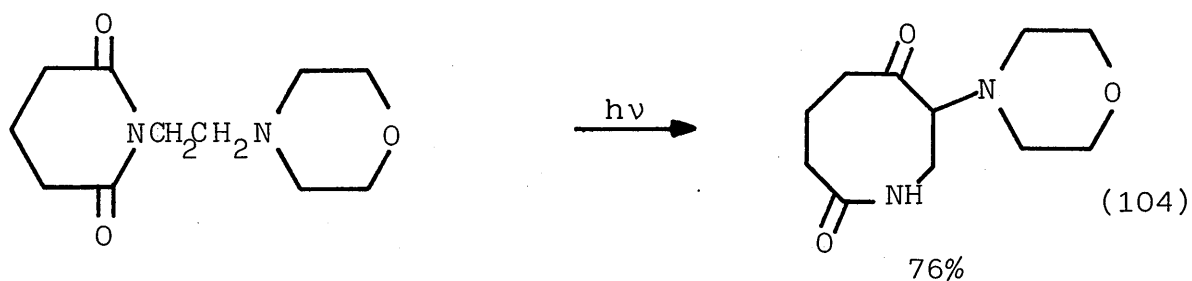


These effects are observed for all the N-(dimethylamino-alkyl)succinimides ($n = 2-6$) and could be attributed to a ground state interaction between the δ -negative amine nitrogen atom with the δ -positive carbon atom of the carbonyl group. This would tend to have a shielding effect (by the δ -positive carbon) on the methylene group adjacent to the amine nitrogen atom.

(a) N-(Dialkylaminoethyl) derivatives

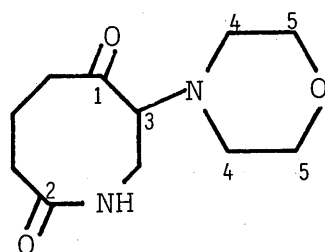
Irradiation of (dialkylaminoethyl)- derivatives of succinimide (98 a and 98 b), glutarimide (99) and 1,2,3,6-tetrahydrophthalimide (100) gave ring expanded products, in yields ranging from 17 to 76% based on unrecovered starting material.





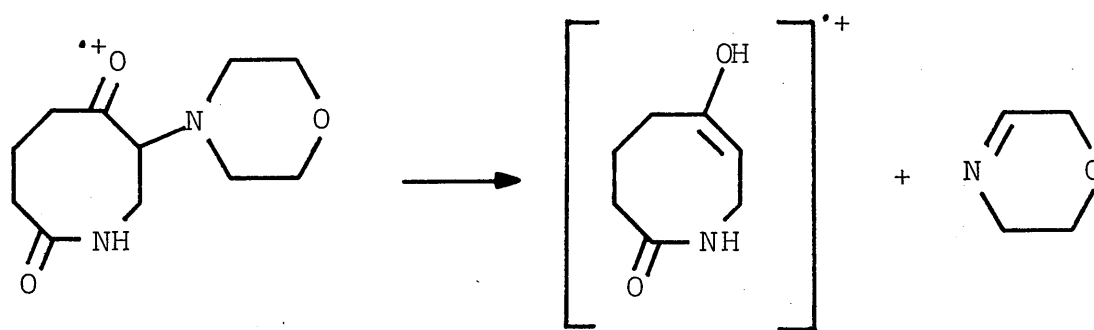
The photoproducts were characterised mainly from their ^{13}C -nmr, infrared and mass spectra. High-resolution mass spectra were obtained instead of elemental analysis, due to the difficulty in purifying semi-solids and gums. ^1H -nmr spectra were obtained for each product, but they gave little extra information because the signals were mainly complex multiplets.

The ^{13}C -nmr spectra show characteristic signals for a ketone carbonyl at $\sim 210 - 220$ ppm, an amide carbonyl at ~ 176 ppm, and a doublet signal at ~ 75 ppm for the methine carbon in the perhydroazepine or perhydroazocine ring directly attached to the amine nitrogen atom. The relative intensities of signals for the carbon atoms of the amine substituent indicate that the morpholino or dimethylamino group is intact and has not taken part in the photochemical reaction e.g.



<u>δ/ppm</u>	
1	213
2	175
3	79(d)
4	70(intense)
5	52(intense)

The infrared spectra show weak absorption bands at 3200 and 3100 cm^{-1} for the amide NH, and strong bands at $\sim 1710\text{ cm}^{-1}$ and $\sim 1670\text{ cm}^{-1}$ for the ketone carbonyl and amide carbonyl respectively. The mass spectra usually give a molecular ion (M^+) and an ion corresponding to the loss of the amine group by a McLafferty rearrangement (106).



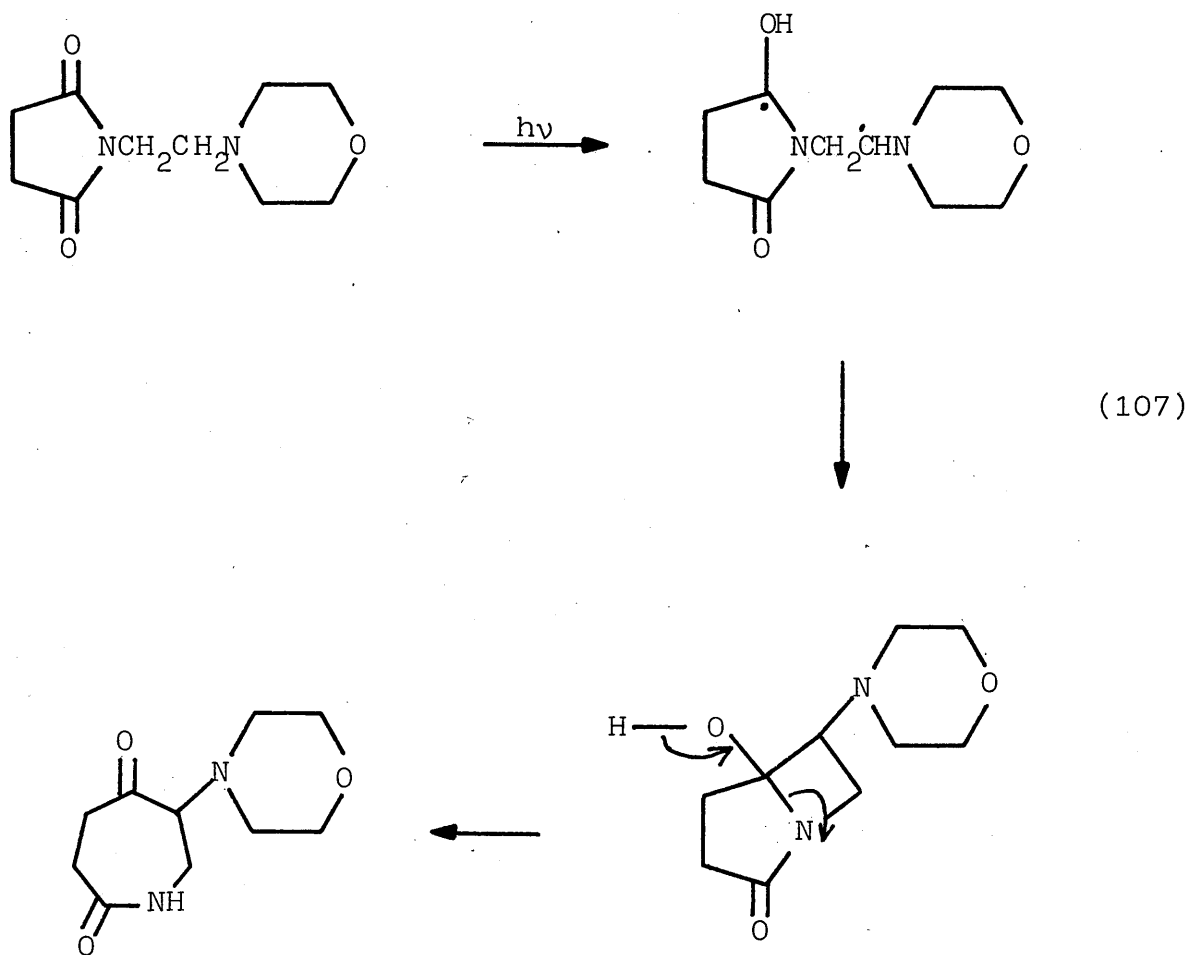
(106)

These ring-expanded photoproducts, which incorporate the two-carbon unit from the side chain, correspond to those derived in low yield from (methylthioalkyl)-succinimide (44 and 45), and also to the major product from the irradiation of N-alkylsuccinimides (42), glutarimides,^{52 - 56} and phthalimides (27).³⁵

The most likely mechanism for the formation of these products involves γ -hydrogen abstraction to give a biradical, cyclisation to a bicyclic-azetidinol intermediate, and cleavage of the N-C(OH) bond (107).

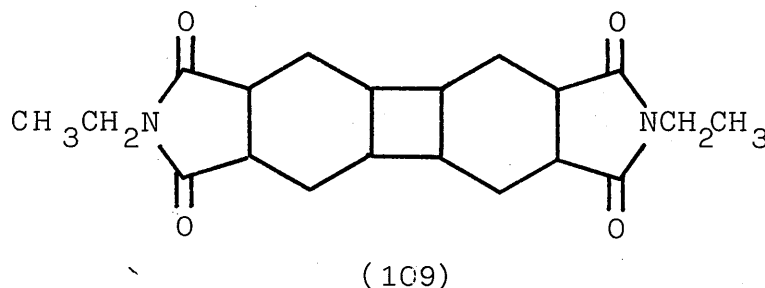
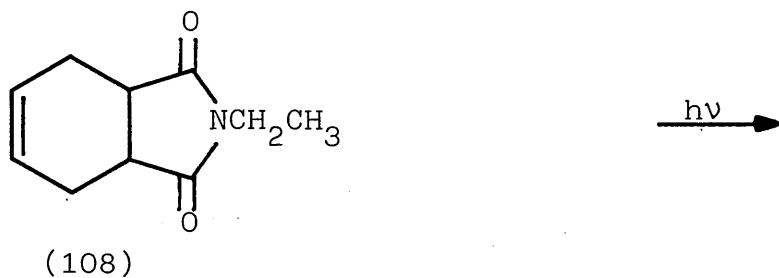
A recent report⁵⁶ has queried the synthetic value of the formation of perhydroazepinediones from N-alkylsuccinimides. Two groups have independently irradiated a series of N-alkylsuccinimides, and observed the same type of photoproduct in yields ranging from 31 - 45%⁵⁴ and 7- 55%⁵⁶ (the next highest yield below 55% was 12%), accompanied by some unsubstituted succinimide (up to 30%). We have based our yields

(17 - 76%) of the photoproducts from N-(dialkylaminoethyl) substrates on unrecovered starting material.



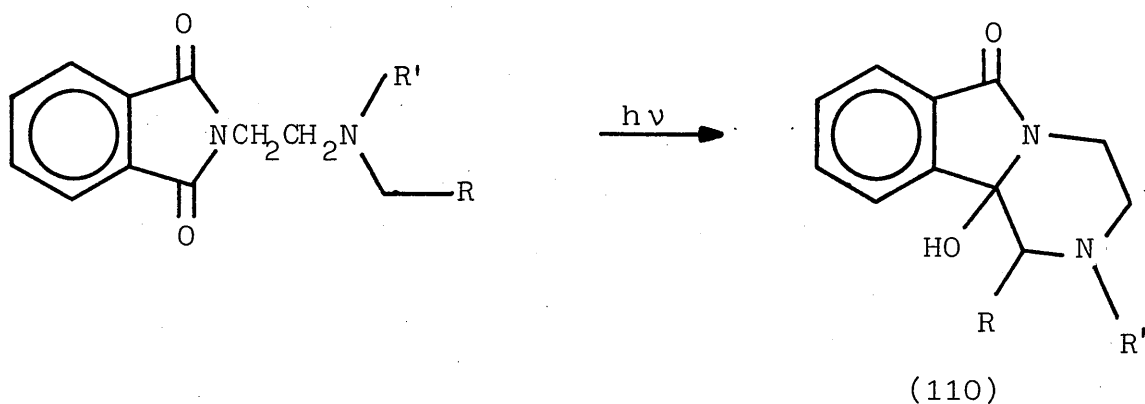
Even so, if the recovered starting material is not taken into account, our yields would still give a range up to 40%. From our irradiations, we did not isolate any of the unsubstituted imide, although for the (dimethylaminoethyl)succinimide (103) there is clearly much unrecovered starting material that is not accounted for. The glutarimide derivative (104) gives an exceptionally high yield of photoproduct, as does the derivative of a bicyclic succinimide

(105). This can be compared with the reported⁵⁶ irradiation of N-ethyl-1,2,3,6-tetrahydrophthalimide (108) which gives only a $[2 + 2]$ dimer of unknown stereochemistry (109).

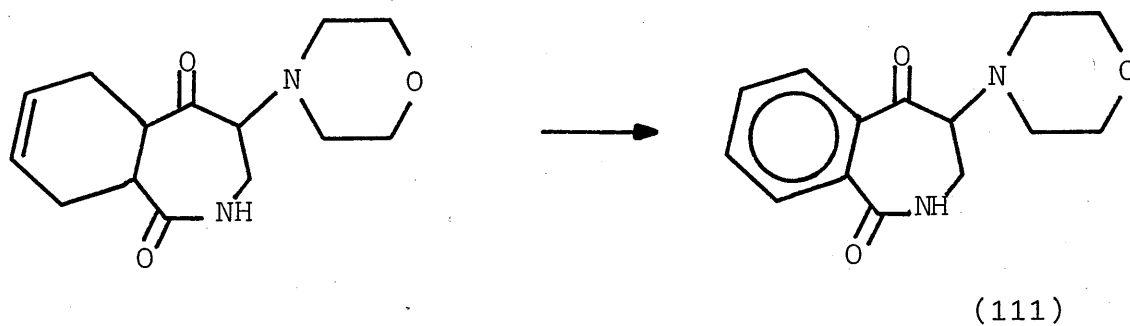


Our results give a strong indication that a heteroatom in the side chain enhances the efficiency of the photoreaction, although the corresponding sulphur analogues gave ring expanded photoproducts in only very low yield.

The ring expansion process is not observed for phthalimide derivatives with a heteroatom in the side chain;⁴⁴ instead, ϵ -hydrogen abstraction, followed by cyclisation is preferred for N-(2-dialkylaminoethyl)phthalimides (110).



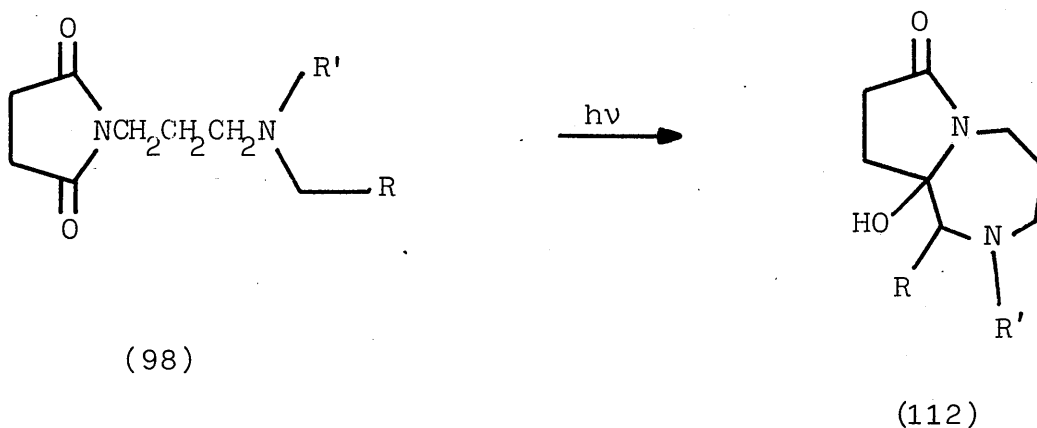
This means that 2-benzazepine-1,5-diones are not accessible photochemically from phthalimides of this type. However, the corresponding tetrahydro derivatives such as (105) are available in good yield by photochemical ring expansion. This opens up the possibility of preparing a benzazepinedione (111) by dehydrogenation.



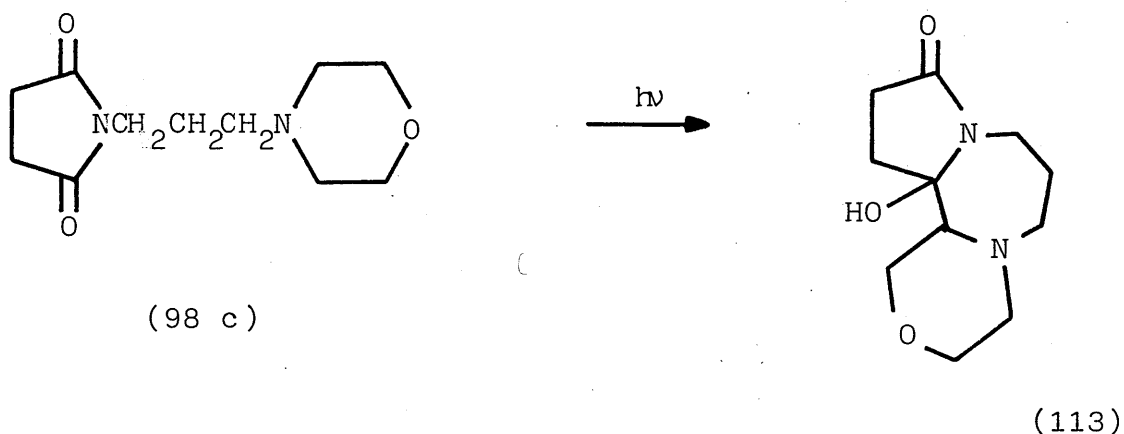
The classical dehydrogenation methods are based on high temperature removal of hydrogen using selenium or metal catalysts.⁹⁹ An alternative method is in the use of benzoquinone reagents, as these offer a procedure which utilises much milder reaction conditions. A reflux of (105) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry benzene gave a complex reaction mixture and separation of the mixture by silica-gel column chromatography gave no dehydrogenated product. The reactivity of the compound under these conditions probably arises from the α -aminoketone structural unit.

(b) N-(Dialkylaminopropyl) derivatives

N-(3-Dialkylaminopropyl)succinimides gave cyclic photoproducts on irradiation with a new 1,4-diazepine ring (112).

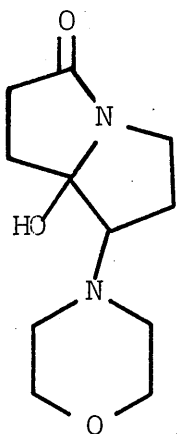


Irradiation of the (dimethylaminopropyl) derivative (98; R = H; R = CH₃) gave the product in 31% yield. The (morpholin-4-ylpropyl) substrate (98 c) gave one diastereoisomer of the product (113) in 12% yield.

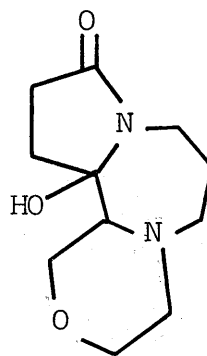


The structural assignment is based on information obtained from the infrared spectrum (absorption bands at 3335 cm⁻¹ (broad) for the hydroxyl group, and at 1685 cm⁻¹ (strong) for the amide carbonyl) and the ¹³C-nmr spectrum (signals at 174.4 ppm for the amide carbonyl, 92.4 ppm for the quaternary carbon (C-OH), and individual signals for the non-equivalent morpholine-derived carbon atoms at 66.7, 66.3, 65.5 and 51.8 ppm). The ¹H-nmr spectrum was recorded, but it gave little extra information because the signals were mainly complex multiplets.

Also isolated from the reaction mixture of (98 c) was a second product (8%) but we could not elucidate the structure from the spectral data. The infrared spectrum showed weak absorption bands around 3250 cm^{-1} , possibly indicating NH and a strong band at 1650 cm^{-1} for a carbonyl group. The ^{13}C -nmr spectrum showed signals at 178.9 ppm for a carbonyl group, and intense signals at 65.8 and 52.7 ppm, suggesting that the morpholine ring is still intact. Other signals in the ^{13}C -nmr spectrum indicate that the product has the same number of carbon atoms as the starting material. Although we could not elucidate the structure of this photoproduct, we can be fairly certain that it is not a photocyclised product, (115) or (116).



(115)

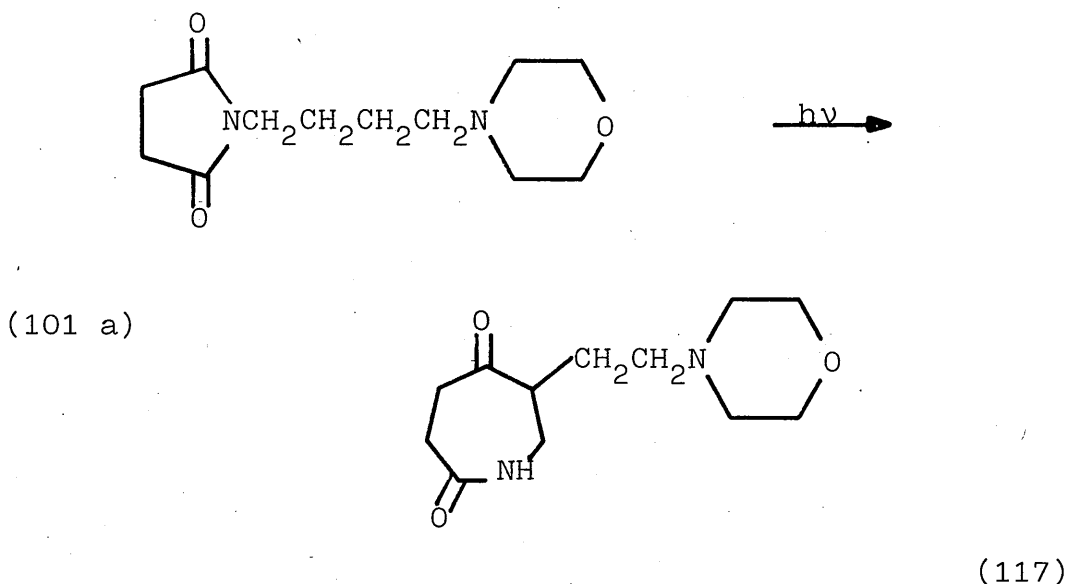


(116)

(116) is ruled out on the basis of an intact morpholine ring and no quaternary carbon (C-OH) (around 85 - 100 ppm), and (115) on the basis of no quaternary carbon (C-OH) and no signal (70 ppm) for a methine carbon directly attached to the amine nitrogen atom.

(c) N-(Dialkylaminobutyl) derivatives

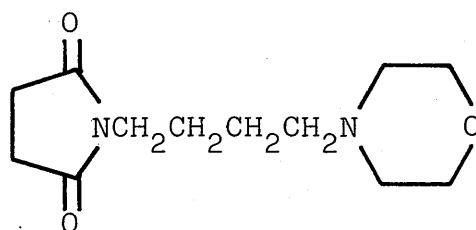
Irradiation of N-[4-(morpholin-4-yl)butyl]succinimide (101 a) gave a mixture of photoproducts. A ring-expanded photoproduct (117, a perhydroazepinedione) was isolated in 26% yield, analogous to the products obtained from N-alkylsuccinimides (42) and N-(2-dialkylaminoethyl)succinimides (98 a and b).



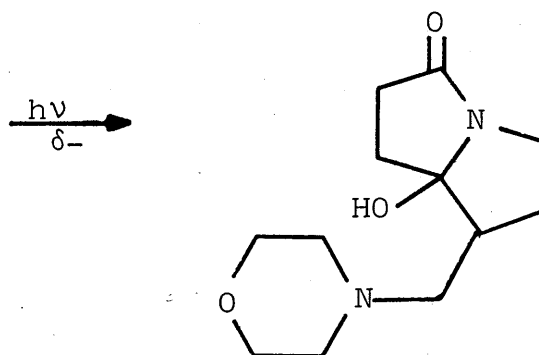
The photoproduct was identified on the basis of its similar characteristic spectral data to those of the photoproduct (102) from N-[2-(morpholin-4-yl)ethyl]-succinimide. The main difference is the lower chemical shift value in the ^{13}C -nmr spectrum for the methine carbon in the perhydroazepinedione ring, 52.2 ppm

in (117), compared with 74.9 ppm in (102).

The second product isolated (13%) was a photocyclised product, as indicated by a single carbonyl signal at 174.5 ppm and a quaternary carbon (C-OH) signal at 97.7 ppm in the ^{13}C -nmr spectrum, and bands in the infrared spectrum at 3300 cm^{-1} (broad) for the hydroxyl group and 1700 cm^{-1} (strong) for the amide carbonyl group. The ^1H -nmr spectrum was recorded but it gave little extra information because the signals were mainly complex multiplets. The formation of cyclic photoproducts could arise by way of δ -(118), ϵ -(119) or ζ -(120) hydrogen abstraction in this particular substrate.

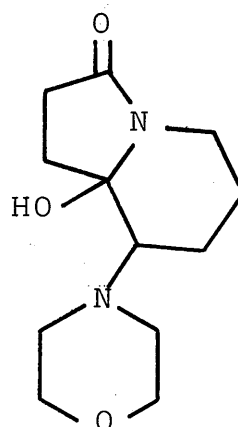
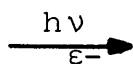


(101 a)



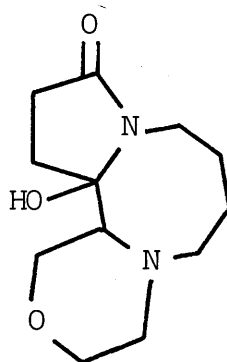
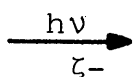
(118)

(101 a)



(119)

(101 a)



(120)

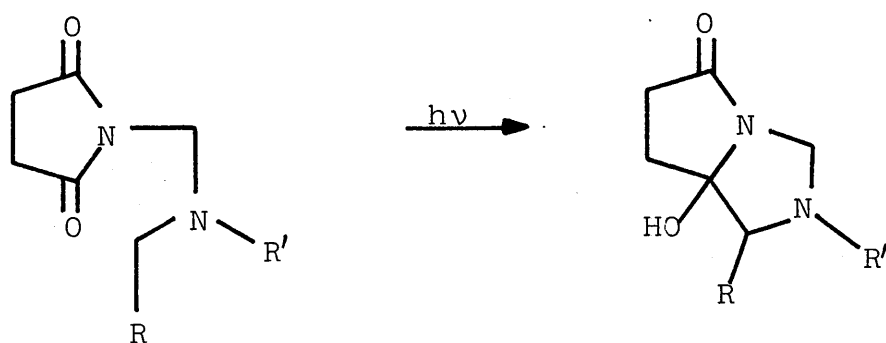
The ^{13}C -nmr spectrum provides the major indication of which methylene group has taken part in the photocyclisation process. Intense signals at 66.9 and 54.3 ppm indicate that an intact morpholine ring is present, which rules out the product of ζ -hydrogen abstraction (120). The methine carbon gives a signal at 44.6 ppm (a doublet in off-resonance). If the product arose by way of ϵ -hydrogen abstraction (119) the resulting methine group directly attached to the nitrogen atom of the morpholine ring would give

a signal at a much higher chemical shift value than 44.6 ppm (cf. N-[3-(morpholin-4-yl)propyl]phthalimide photoproduct, chapter 4, where a similar carbon atom gives rise to a signal at 69.2 ppm). This, therefore, gives a strong indication that the product is the one in which a new five-membered ring has been formed (118).

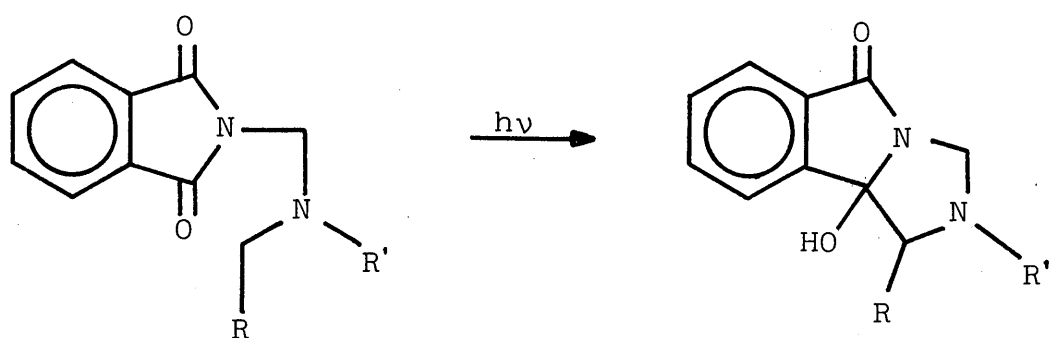
N-(4-Dimethylaminobutyl)- (101 b) and N-(5-dimethylamino-pentyl)succinimide (101 c) were also irradiated, but no identifiable photoproducts could be isolated from the reaction mixtures.

These photochemical reactions of (dialkylaminoalkyl) derivatives of succinimide and glutarimide show that there is a difference in their photochemical cyclisation processes when compared with reactions of the corresponding phthalimide substrates.

We have shown that Mannich bases of alicyclic imides undergo photochemical cyclisation to give products with a new imidazolidine ring (121), and these products correspond to the photoproducts isolated from phthalimide Mannich bases (122).

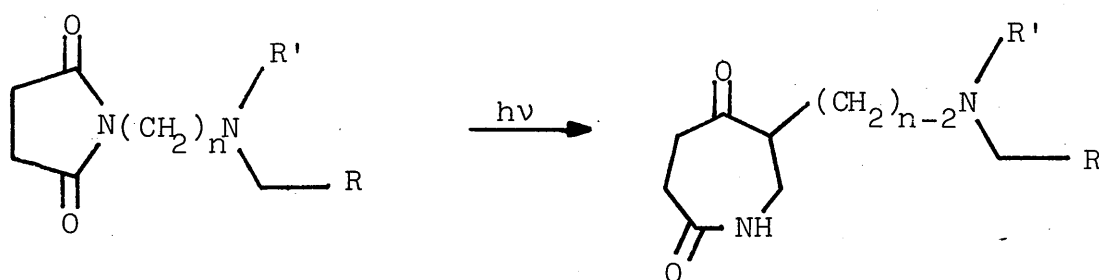


(121)

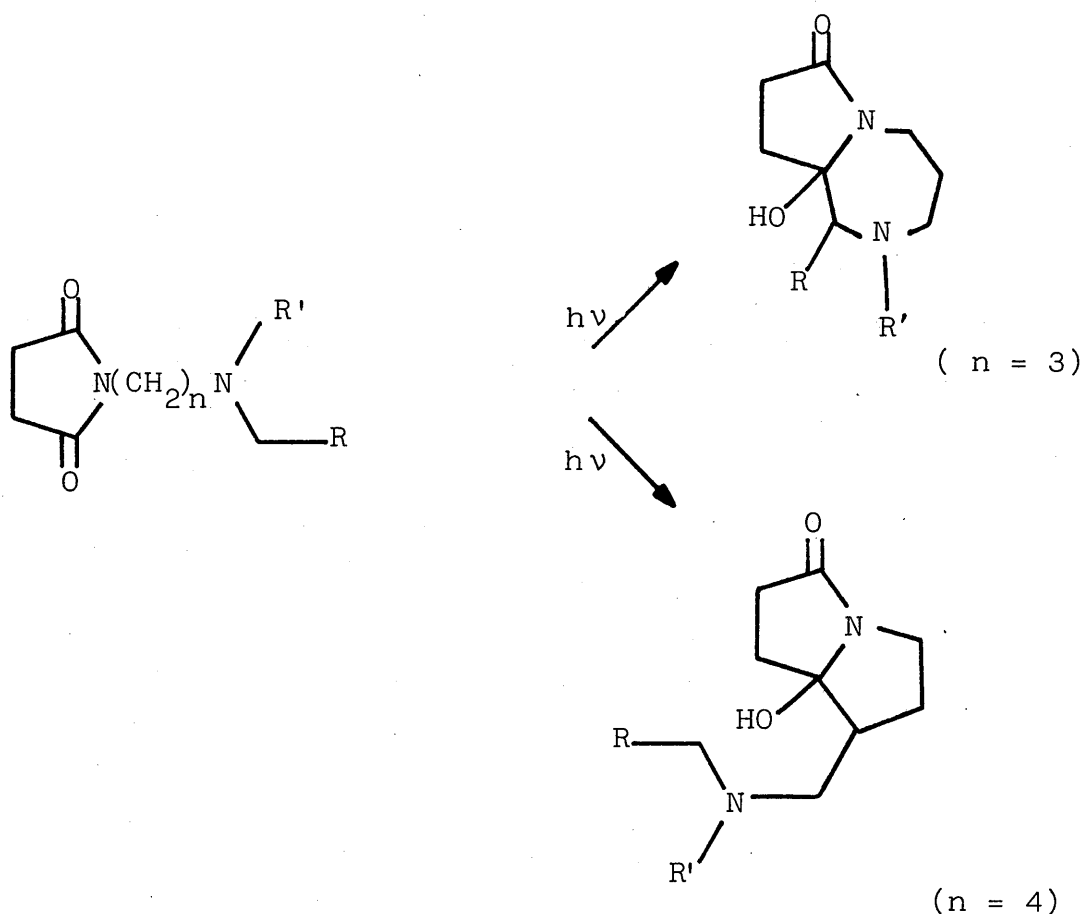


(122)

The differences between the alicyclic and aromatic imides toward cyclisation becomes apparent when the alkyl chain between the imide nitrogen atom and the amine nitrogen atom is increased in length. Phthalimide substrates have been shown to give photo-cyclised products with new rings containing up to 16 atoms. The alicyclic imide derivatives that we have investigated give ring expanded products when $n = 2$ or 4 , bicyclic diazepine derivatives when $n = 3$ and bicyclic pyrrolidine products when $n = 4$.

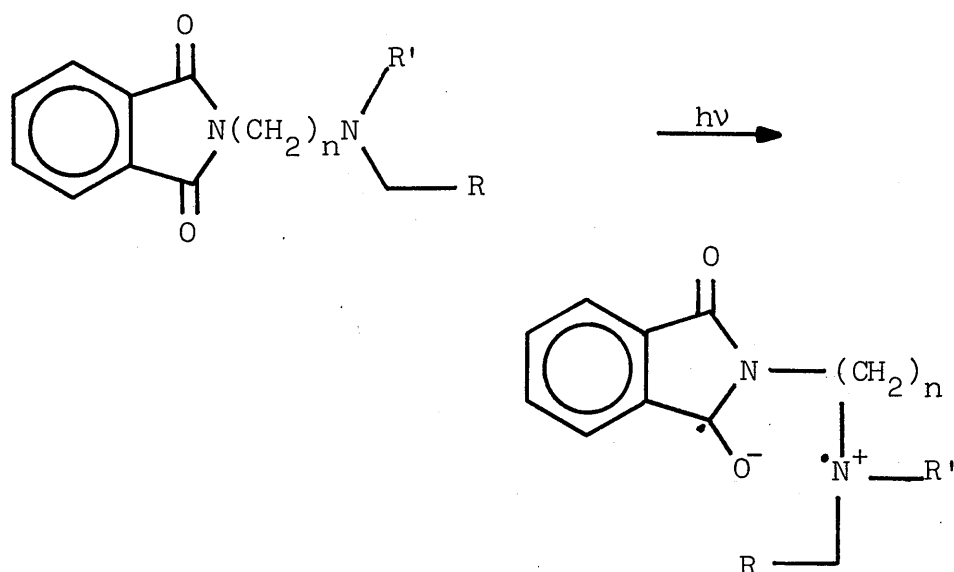


($n = 2$ or 4)

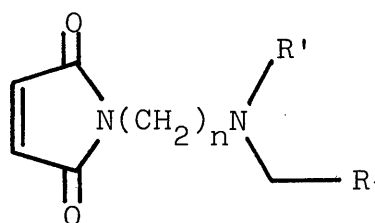


It seems that the aromatic ring of phthalimides enhances formation of medium and large ring products. This could be because the aromatic ring is a good electron acceptor, and charge-transfer interaction in the excited state leads to preferential conformations of the molecule in which the terminal heteroatom (δ^+) and the imide (δ^-) are in close proximity.

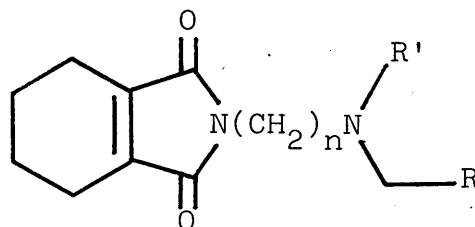
This mechanism appears very reasonable when considering the formation of macrocyclic rings with up to 38 atoms from non-rigid systems.



The aliphatic imides are poorer electron acceptors, and it may be that efficient charge-transfer does not occur, so that macrocyclic ring systems may not be possible from such substrates. As a test of this hypothesis, we have prepared and irradiated some N-(dialkylaminoalkyl) imides which have a double-bond conjugated with the carbonyl group, namely maleimides (123) and 3,4,5,6-tetrahydrophthalimides (124).



(123)



(124)

These imides are better electron acceptors than the corresponding saturated imides, and their photochemistry may bear a greater resemblance to that of phthalimides. The results are discussed in chapter 4.

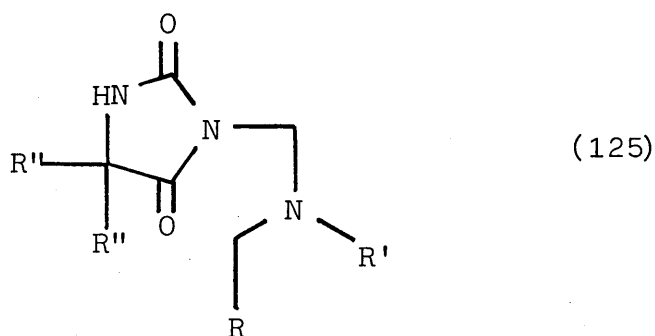
C H A P T E R T H R E E

THE RESULTS AND DISCUSSION FOR THE HYDANTOIN,
5,5-DISUBSTITUTED HYDANTOINS AND DIHYDRO-
URACIL DERIVATIVES

Irradiation of Mannich bases derived from 2-phenyl-succinimide gives mixtures of cyclised photoproducts in which cyclisation has occurred at either the C-1 or C-4 carbonyl group. Based on the ratios of the amounts of products isolated, the preferred orientation of cyclisation (by a factor of about 6 to 1) is to the C-1 carbonyl group (adjacent to the CH-Ph group). Accordingly, we have studied the photochemical cyclisation of Mannich bases derived from hydantoin, 5,5-disubstituted hydantoins and dihydrouracil to see if there is a greater selectivity in the orientation of cyclisation for these substrates, and our results and discussion are described in this chapter.

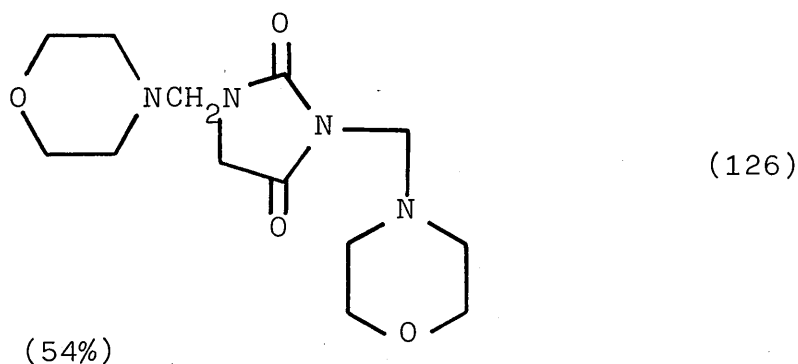
N-(Dialkylaminomethyl) derivatives (Mannich bases)

Mannich bases of hydantoin and 5,5-disubstituted hydantoins have been reported previously^{75,82} and are easily prepared using the method described for succinimide Mannich bases. All are crystalline solids which readily precipitate from the reaction mixture, and the substrates prepared and the yields obtained are listed below:



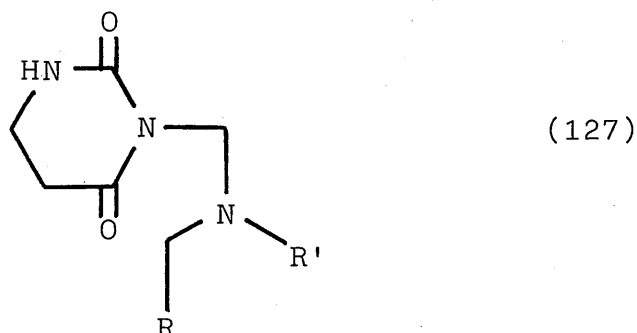
- | | |
|---|-------|
| (a) $R'' = H$; $R, R' = CH_2OCH_2CH_2$ | (72%) |
| (b) $R'' = CH_3$; $R, R' = CH_2OCH_2CH_2$ | (71%) |
| (c) $R'' = Ph$; $R, R' = CH=CHCH_2CH_2$ | (76%) |
| (d) $R'' = Ph$; $R, R' = o-C_6H_4CH_2CH_2$ | (77%) |
| (e) $R'' = Ph$; $R, R' = CH_2OCH_2CH_2$ | (78%) |
| (f) $R'' = Ph$; $R = H$; $R' = CH_3$ | (73%) |

Reaction of hydantoin with excess formaldehyde and morpholine gave a bis Mannich base (126). This product has been reported previously.⁸²



Mannich bases from dihydrouracil are not as easily prepared, and we have found no examples of these compounds in the literature. Attempted preparation by the same method employed for the succinimide Mannich bases usually gave recovered dihydrouracil. A bis(dialkylamino)methane (63) was also isolated when 1,2,3,4-tetrahydroisoquinoline was employed as the secondary amine. To overcome this problem, we employed the method used for the preparation of glutarimide Mannich bases. The products were prepared in the absence of solvent, although methanol had to be added to the reaction mixture of (127 b) to form a homogeneous solution. All the Mannich bases of dihydrouracil were purified as hydrochloride

salts, and subsequent neutralisation with aqueous sodium bicarbonate regenerated the Mannich base. All the products were of the general structure (127) with no bis Mannich bases of the type (126). The Mannich bases of dihydrouracil and the yields obtained are listed below:



- | | |
|---|-------|
| (a) R, R' = CH ₂ OCH ₂ CH ₂ | (68%) |
| (b) R, R' = o-C ₆ H ₄ CH ₂ CH ₂ | (64%) |
| (c) R, R' = CH=CHCH ₂ CH ₂ | (69%) |
| (d) R, R' = (CH ₂) ₄ | (62%) |

A number of spectral properties are characteristic of the Mannich bases. In the infrared spectra there are two carbonyl stretching bands at 1710 and 1770 cm⁻¹ for hydantoins, or at 1680 and 1730 cm⁻¹ for dihydrouracils, which are also observed for the unsubstituted parent compounds. The NCH₂N group in the Mannich base gives rise to signals in the ¹H- and ¹³C-nmr spectra near 4.5 and 60 ppm respectively for the hydantoin substrates, and 4.2 and 68 ppm respectively for the dihydrouracil substrates. In the ¹³C-nmr spectra there are two carbonyl signals at 173 ppm (C-4, compare 180 ppm for succinimide), and 158 ppm (C-2, compare 165 ppm for urea) for

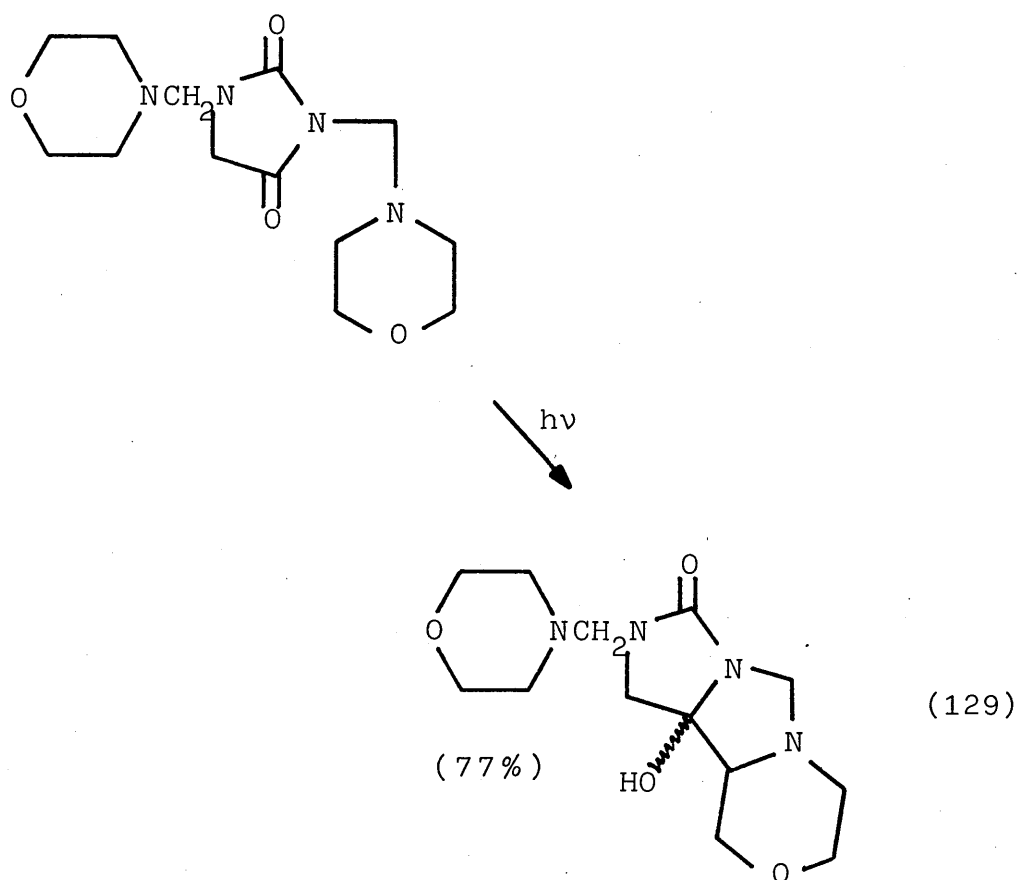
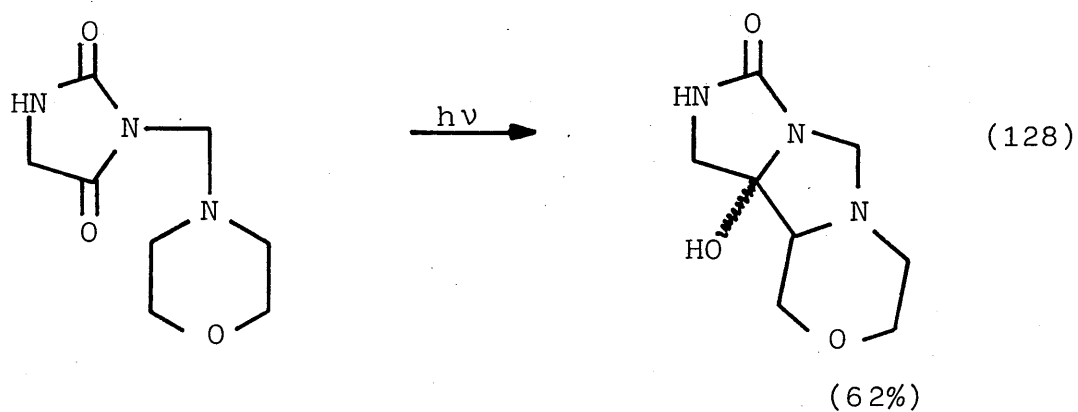
hydantoins, and at 170 and 153 ppm for dihydrouracils. From the ^{13}C -nmr chemical shift values for the carbonyl groups, we can deduce that the Mannich reaction has occurred at N-3 in the hydantoins, by comparing the ^{13}C -nmr data for the mono Mannich bases with those for the unsubstituted hydantoin (179 and 163 ppm). We would expect that substitution at N-1 would affect predominantly the chemical shift value for the C-2 carbonyl, but substitution at N-3 would affect (as is observed) the chemical shift values for both C-2 and C-4 carbonyl signals.

As with succinimide Mannich bases, the hydantoin and dihydrouracil substrates cannot give analogues of perhydroazepinediones on irradiation, as N-alkylimides do (42); this is because the γ -position is occupied by a tertiary nitrogen atom. However, (124, 126 and 127) could give rise to photocyclised products by reaction at the position adjacent to the amine nitrogen atom, i.e. the δ -position.

The conditions used for the irradiations of hydantoin and dihydrouracil Mannich bases are the same as described for the succinimide Mannich bases in chapter 2.

Irradiation of 3-(morpholin-4-ylmethyl)hydantoin and 1,3-bis(morpholin-4-ylmethyl)hydantoin (125 a and 126) each gave two major photoproducts (in 62% and 77% combined yields, respectively, based on unrecovered starting material). The photoproducts from (125 a) could not be separated by column chromato-

graphy, although one of the diastereoisomers was isolated by partial crystallisation from chloroform. The major photoproducts (128 and 129) are two diastereoisomeric compounds with a new imidazolidine ring.



From each reaction mixture, hydantoin (44 and 37% respectively) was also isolated, and this could possibly have been produced by a direct β -cleavage reaction in the excited state.

The structures of the photoproducts were assigned on the basis of microanalytical results and spectroscopic properties. The elemental analysis results show that the photoproducts are isomeric with the Mannich bases. For (129), where a pure sample of the photoproduct could not be prepared a high-resolution mass spectrum was obtained. The mass spectrum showed a molecular ion (M^+) corresponding to the molecular formula of the substrate. The spectrum also showed loss of water ($M^+ - H_2O$) and a base peak corresponding to $C_5H_{10}NO$.

Other spectroscopic properties of the photoproducts support the structural assignment as diastereoisomers of 1,3,7-triazabicyclo[3.3.0]octanes from hydantoin Mannich bases. The infrared spectra show an absorption band at 3300 cm^{-1} (usually broad) for the hydroxyl group and a single carbonyl group at 1700 cm^{-1} , indicating that cyclisation has occurred at the C-4 carbonyl group. As with the photoproducts from succinimide Mannich bases, we would expect to observe a pair of doublets in the 1H -nmr spectra arising from the cyclic NCH_2N group of the imidazolidine ring. Only in the case of one diastereoisomer of (128) do we observe both doublets at 4.55 and 4.04 ppm. The second isomer of (128) could not be obtained

as a pure component, but the ^1H -nmr spectrum of a mixture of diastereoisomers of (128) shows a doublet at 4.87 ppm (which is not observed in the spectrum of the isolated isomer) with a coupling constant of 8 Hz. The second half of the pattern of two doublets cannot be seen because of the complexity of the spectrum between 4.0 and 3.0 ppm. In the ^1H -nmr spectra of both diastereoisomers of (129) only the lower field doublet can be observed at 4.35 and 4.84 ppm. The remainder of the ^1H -nmr spectra are very complex and assignment of the signals is difficult.

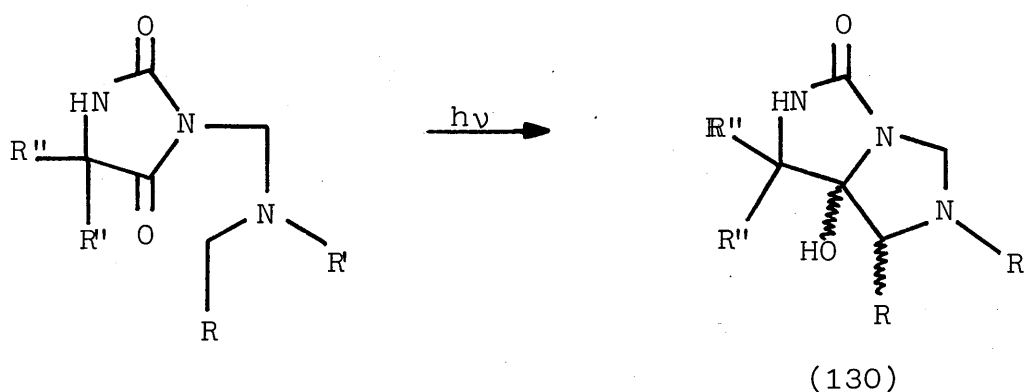
The ^{13}C -nmr spectra of the diastereoisomers of (128) and (129) show a single carbonyl signal at 164.2 and 166.4 ppm, and 161.2 and 164.4 respectively, a quaternary carbon atom (C-OH) at 93.9 and 95.0 ppm, and 90.5 and 92.2 ppm respectively and a signal at approximately 66 ppm corresponding to the carbon atom of the NCH_2N group. From the chemical shift values of the carbonyl signals, we can be fairly confident that cyclisation has occurred at the C-4 carbonyl group and not at C-2. In the ^{13}C -nmr spectrum of (129) there are also intense signals at 67 and 51 ppm, indicating that the morpholine ring at N-1 is intact. We did not find any evidence for photoproducts where a second cyclisation had occurred at the C-2 carbonyl group. This suggests that the excited states of the hydantoin and the urea-like product are different in their reactivity.

We determined the stereochemistry of the succinimide photoproducts (chapter 2) by comparing their spectral data with those for the corresponding photoproducts derived from phthalimide, where X-ray crystallographic confirmation of structure has been obtained. The information for the hydantoin photoproducts (128) and (129) is less extensive. However, one isomer has a lower chemical shift value for the lower field signal arising from a hydrogen atom of the NCH_2N group (4.55 or 4.35 ppm for one isomer, compared with 4.87 or 4.84 ppm for the other isomer), a smaller coupling constant for the geminal hydrogen atoms of the NCH_2N group in the ^1H -nmr spectra (4/5 Hz, compared with 8 Hz) and a lower chemical shift value for the quaternary carbon atom (C-OH) in the ^{13}C -nmr spectra (93.9 or 90.5 ppm for one isomer, compared with 95.0 or 92.2 ppm for the other isomer); these all suggest that this isomer has the bridgehead OH and H groups cis with respect to each other.

The diastereoisomers of (128) and (129) could be isolated as single components, but they were slowly converted to a mixture of stereoisomers on standing in solution. It seems most likely that this occurs by cleavage and reformation of the (HO)C-N(CO) bond but we have no explanation of why it does not happen for the corresponding succinimide photoproducts.

5,5-Disubstituted hydantoin Mannich bases

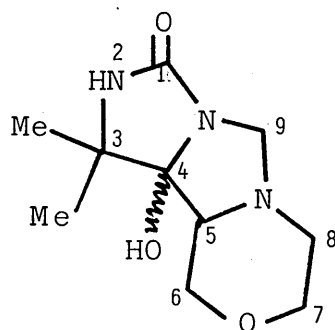
Irradiation of 3-(dialkylaminomethyl)-5,5-dimethyl or 5,5-diphenylhydantoins gave one major photoproduct (in 36 to 72% yield based on unrecovered starting material) which could be isolated by column chromatography. The major photoproducts (130) are 1,3,7-triazabicyclo[3.3.0]octanes, which contain a new imidazolidine ring.



- | | |
|--|-------|
| (a) $R'' = \text{CH}_3$; $R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$ | (60%) |
| (b) $R'' = \text{Ph}$; $R, R' = \text{p-C}_6\text{H}_4\text{CH}_2\text{CH}_2$ | (72%) |
| (c) $R'' = \text{Ph}$; $R, R' = \text{CH=CHCH}_2\text{CH}_2$ | (42%) |
| (d) $R'' = \text{Ph}$; $R, R' = \text{CH}_2\text{OCH}_2\text{CH}_2$ | (36%) |
| (e) $R'' = \text{Ph}$; $R = \text{H}$; $R' = \text{CH}_3$ | (52%) |

The structures of the photoproducts were assigned on the basis of microanalytical results and spectroscopic properties. The elemental analysis results showed that the photoproducts are isomeric with the Mannich bases. In some cases elemental analysis did not

give good results, due to the difficulty of purifying small quantities of photoproducts, so high-resolution mass spectra were obtained for these samples. The mass spectra usually gave a molecular ion (M^+) corresponding to the correct molecular formula; they also gave a peak for the loss of water ($M^+ - H_2O$) and a base peak corresponding to the radical ion (69). These last two peaks can most easily be accounted for on the basis of the photocyclised structure. Only in the case of (130 c) was there no molecular ion peak. The other spectroscopic properties of the photoproducts were similar to those of the hydantoin photoproducts. The infrared spectra show an absorption band near 3300 cm^{-1} for the hydroxyl group, and a strong band near 1710 cm^{-1} for the urea-like carbonyl group, indicating that cyclisation has occurred at the C-4 carbonyl group. The ^1H -nmr spectra show the characteristic doublets in the ranges 4.95 - 4.33 ppm and 4.39 - 3.77 ppm for the hydrogen atoms of the cyclic NCH_2N group. The remainder of the ^1H -nmr spectra are very complex and it is difficult to assign the signals. We have obtained a medium-field (220 MHz) ^1H -nmr spectrum of the photoproduct (130 a) and have attempted to assign the signals using molecular models to estimate coupling constants.



(130 a)

7.2	broad, 1H
5.0	very broad, 1H
4.50	d, J=5 Hz, 1H
4.33	dd, J=11 and 3 Hz, 1H
4.23	d, J=5 Hz, 1H
4.01	t, J=10½ Hz, 1H
3.84	dd, J=11 and 3 Hz, 1H
3.57	td, J=11 and 3 Hz, 1H
2.92	broad d, J=11 Hz, 1H
2.74	dd, J=10 and 3 Hz, 1H
2.54	td, J=11 and 3 Hz, 1H
1.64	s, 3H
1.42	s, 3H

This assignment must be regarded as tentative although we can be fairly certain that the broad signals at 7.2 and 5.0 ppm arise from the NH and OH groups, the pair of doublets at 4.50 and 4.23 ppm arises from the NCH_2N protons 9 and 9', and the singlets at 1.64 and 1.42 ppm arise from the methyl groups at C-3.

The methine hydrogen 5, and the methylene hydrogens 6 and 6', would each be expected to give doublet of doublet signals, and we tentatively assign the doublet of doublets at 4.33 ppm (geminal coupling constant 11 Hz, and cis coupling constant 3Hz) to hydrogen 6, the 4.01 triplet, (geminal and trans coupling constants 10½ Hz) to hydrogen 6', and the 2.74 doublet of doublets (trans coupling constant 10 Hz, and cis coupling constant 3Hz) to hydrogen 5. The other

signals arise from hydrogens 7, 7', 8 and 8', and we would expect the hydrogens adjacent to oxygen to be at higher chemical shift value than the hydrogens adjacent to nitrogen. Hence we assign the signals at 3.84 and 3.57 ppm to hydrogens 7 and 7', and those at 2.92 and 2.54 ppm to hydrogens 8 and 8'. (The coupling patterns are almost right for 7, 7', 8 and 8': $J_{7,7'}=11$ Hz, $J_{7,8}=3$ Hz, $J_{7,8'}=0$ Hz, $J_{7',8}=11$ Hz, $J_{7',8'}=3$ Hz, $J_{8,8'}=11$ Hz).

The ^{13}C -nmr spectra of the photoproducts (130) show a single carbonyl signal near 162 ppm, and again this indicates that cyclisation has occurred at the imide-like carbonyl group C-4. Also in the ^{13}C -nmr spectra is a signal near 98.5 ppm, characteristic of the quaternary carbon atom (C-OH).

Because only one diastereoisomer of the photoproducts (130) was isolated we cannot assign the stereochemistry of the bridgehead OH and H groups from the spectral data as for the succinimide photoproducts. However, there is some evidence from the ^1H -nmr spectrum of (130 b) that the stereochemistry of the OH/H groups is trans. A doublet in the ^1H -nmr spectrum at 5.38 ppm (1H) collapses to a singlet by selective decoupling at 6.7 ppm, and hence the signal arises from a highly shielded aromatic proton. From molecular models of the two isomers of this photoproduct we observe that the C-8 of the tetrahydroisoquinoline unit is close to the π electrons of one of the phenyl rings for the trans isomer, but not for the cis.

Molecular models of the cis isomers of the photoproducts (130) show severe steric interactions between one of the 5-substituents on the hydantoin ring and the amine unit, and this may account for the absence of the cis isomers.

Dihydrouracil Mannich bases

Irradiation of 3-(morpholin-4-ylmethyl)dihydrouracil (127 a) and 3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-dihydrouracil (127 b) gave some minor photoproducts, but the substrates appeared to be photochemically more stable than the corresponding hydantoins. Long irradiation times led to only low conversions and none of the minor products was isolated. There is no obvious reason for this lower reactivity; glutarimide Mannich bases show much the same reactivity as succinimide derivatives, so the behaviour of dihydrouracils cannot be attributed simply to ring size.

From our studies, we have found that Mannich bases of hydantoin or 5,5-disubstituted hydantoins give good yields of photocyclised products with a new imidazolidine ring. Cyclisation occurs at the C-4 carbonyl group only, and there is no evidence for a double cyclisation with the hydantoin bis Mannich base. Mono and bis Mannich bases of hydantoin give two diastereoisomers of the product, but 5,5-disubstituted hydantoin Mannich bases give only one diastereoisomer with the bridgehead OH and H groups trans with respect to each other.

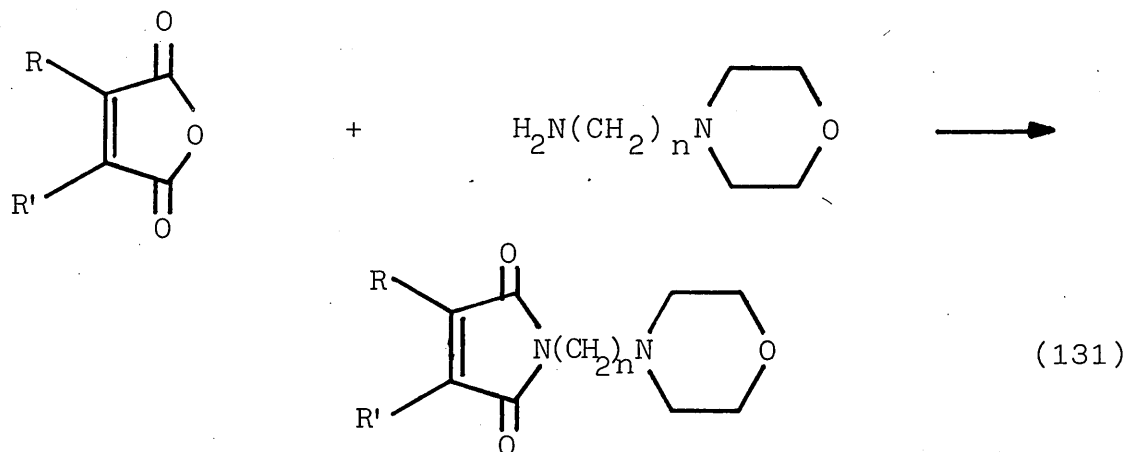
C H A P T E R F O U R

THE RESULTS AND DISCUSSION FOR MALEIMIDE
AND PHTHALIMIDE DERIVATIVES

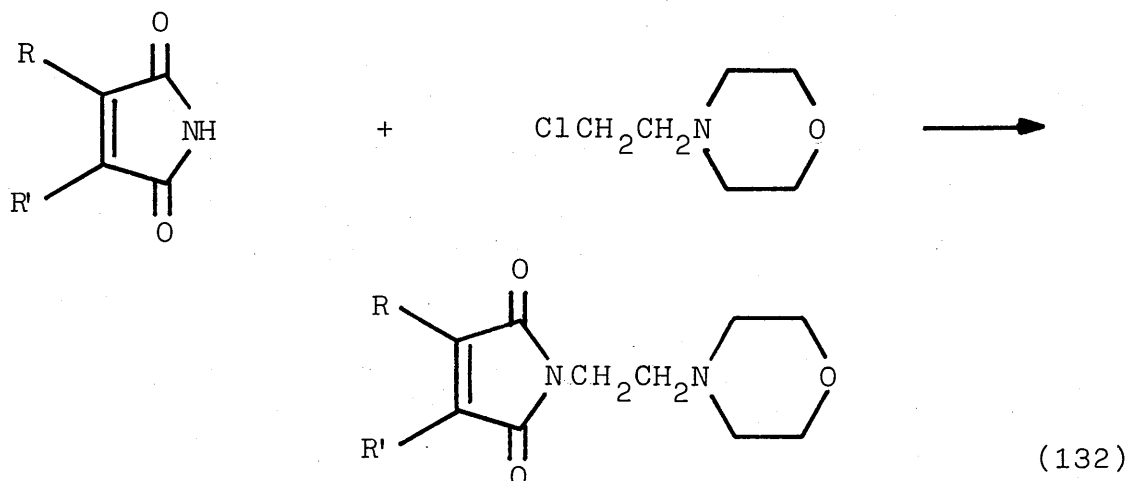
It has been reported that irradiation of N-substituted phthalimide derivatives can give medium/large ring polycyclic heterocyclic systems by a photocyclisation process⁴⁷, and from our own studies of related saturated cyclic imides we have found that these are less efficient in the photochemical formation of compounds with ring sizes greater than five atoms. Our hypothesis is that aromatic imides can undergo a photochemical electron-transfer process, which enhances cyclisation and the formation of medium/large ring products, but the alicyclic imides, which are less efficient electron acceptors, do not as readily undergo such a process. This led us to study some unsaturated, non-aromatic imides, to see if they would give photocyclisation products with ring sizes greater than five atoms, and for comparison we also irradiated the corresponding phthalimide derivatives.

N-(Dialkylaminoalkyl) derivatives

The substrates were prepared either by the reaction of the anhydride with a primary (aminoalkyl)amine, or of the imide with a primary (chloroalkyl)amine:



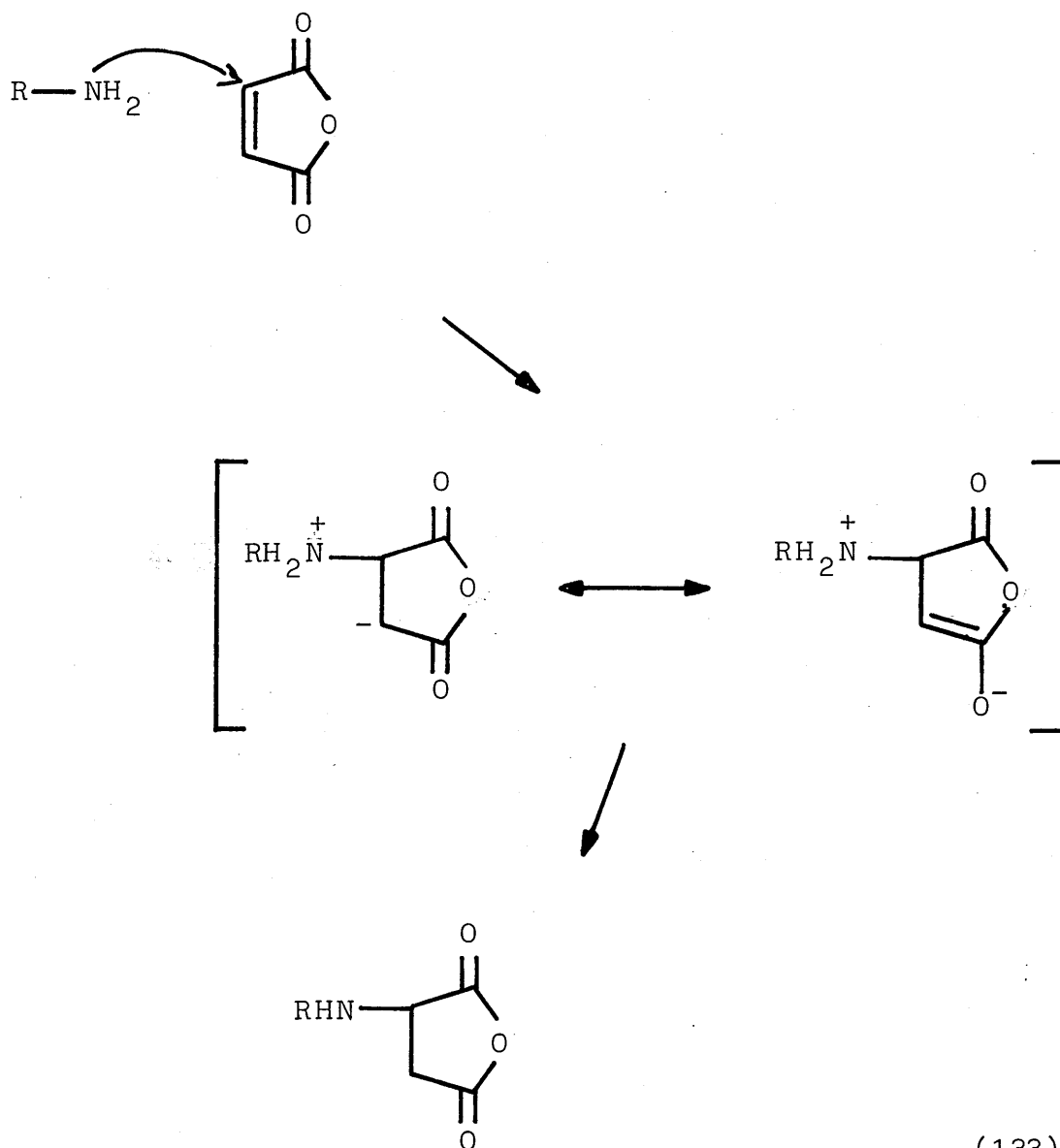
- (a) $n = 2$; $R, R' = (CH_2)_4$ (61%)
 (b) $n = 3$; $R, R' = (CH_2)_4$ (55%)
 (c) $n = 3$; $R, R' = CH=CHCH=CH$ (62%)



- (a) $R, R' = H$ (31%)
 (b) $R, R' = CH=CHCH=CH$ (77%)

The substrates prepared from phthalimide or from 3,4,5,6-tetrahydrophthalimide that did not crystallise from the reaction mixture were purified as hydrochloride salts, and subsequent neutralisation gave the free base. N-[2-(morpholin-4-yl)ethyl]maleimide was prepared from the reaction of maleimide and N-(2-chloroethyl)morpholine, and purified by column chromatography.

This method of preparation was chosen because of competing nucleophilic addition of amines to the alkene conjugated to the carbonyl groups.¹⁰⁰



(133)

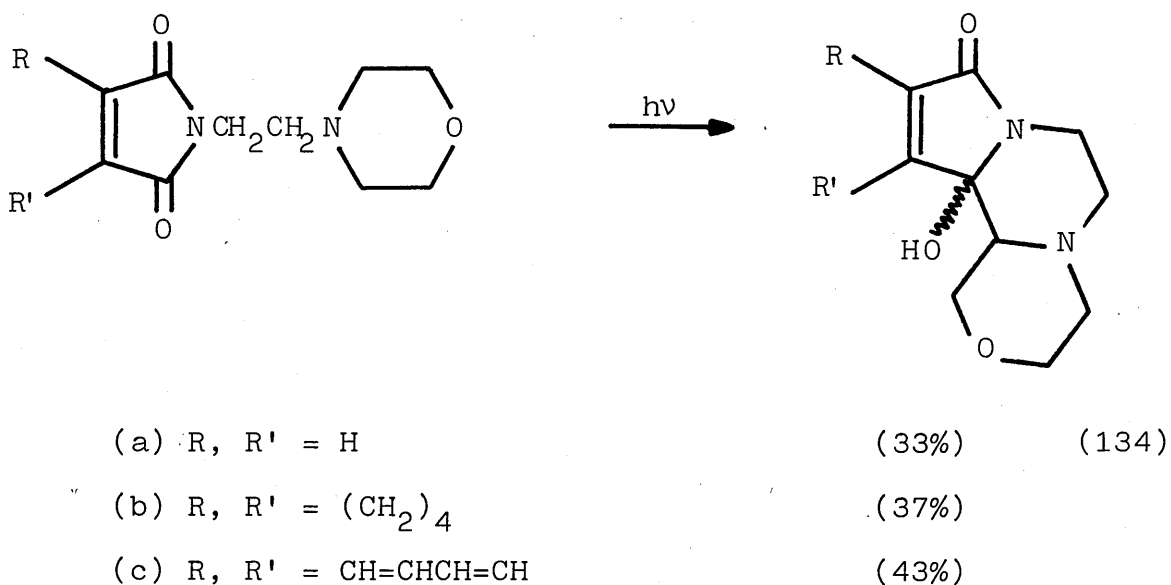
The spectral characteristics of the N-(dialkylamino-alkyl) substrates ($n = 2$ or 3) of phthalimide, 3,4,5,6-tetrahydrophthalimide and maleimide are similar to those of the corresponding succinimide derivatives, but with added bands in the infrared spectra and signals in the 1H -nmr and ^{13}C -nmr spectra for the aromatic and unsaturated $C=C$ groups. The infrared spectra show weak absorption bands at $\sim 1600\text{ cm}^{-1}$ for the aromatic ring, 3100 and 1650 cm^{-1} for the

alkene part of the unsaturated imides (only 1650 cm^{-1} band for 3,4,5,6-tetrahydrophthalimide substrates), and bands at 1770(w) and 1710(s) cm^{-1} for the imide carbonyl groups. The ^1H -nmr spectra show signals at 7.7 ppm for the aromatic protons, and a singlet at ~ 6.7 ppm for the alkene protons in the maleimide. There is no singlet at ~ 4.5 ppm for an NCH_2N group, but signals at higher field (3.8 and 1.7 ppm) correspond to the protons in the N-alkyl chain. The ^{13}C -nmr spectra for succinimide substrates show a signal at 177 ppm for the carbonyl carbon atoms, and this chemical shift value decreases to 171 ppm (3,4,5,6-tetrahydrophthalimide and maleimide) or 168 ppm (phthalimide) as the degree of unsaturation increases. Further signals are observed in the ^{13}C -nmr spectra at, 134 - 123 ppm for the aromatic carbons, 141 and 134 ppm for the alkene carbon atoms of 3,4,5,6-tetrahydrophthalimide and maleimide respectively, intense signals at 67 and 54 ppm for the carbon atoms of the morpholine ring, and signals at 56 - 25 ppm correspond to the carbon atoms in the N-alkyl chain.

Irradiations were carried out using the same conditions as for the succinimide substrates, except that the phthalimide derivatives were irradiated using a Pyrex filter which absorbs shorter wavelength light (≤ 280 nm) from the lamp output. The irradiations were monitored by thin layer chromatography, and the reaction mixtures separated by silica-gel column chromatography.

N-[2-(Morpholin-4-yl)ethyl]-derivatives

Irradiation of the N-[2-(morpholin-4-yl)ethyl]-substrates gave in each case two diastereoisomers of a product with a new piperazine ring (134); yields are based on unrecovered starting material.



The structures of the photoproducts were assigned on the basis of spectroscopic properties.

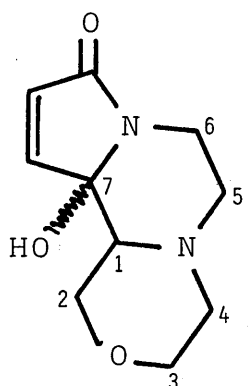
The spectral data for these photoproducts are very similar to those for the cyclised products obtained from the N-(dialkylaminomethyl)succinimides except for the absence of the characteristic NCH₂N signals in the ¹H-nmr and ¹³C-nmr spectra, and the presence of signals corresponding to the NCH₂CH₂N atoms.

The infrared spectra show a strong absorption band near 1700 cm^{-1} for a cyclic five-membered amide carbonyl group, a broad band near 3350 cm^{-1} for the hydroxyl group, and weak bands near 1600 cm^{-1} or 1640 cm^{-1} for aromatic or unsaturated groups respectively. ^1H -nmr spectra were very complex although an indication that cyclisation had occurred at the ϵ -position came from the absence of strong multiplet signals characteristic of an intact morpholine ring. The ^{13}C -nmr spectra were of greatest help in elucidating the structures; they showed signals characteristic of a cyclised photoproduct near 170 ppm for a single carbonyl carbon atom, 86 ppm for a quaternary carbon atom (C-OH), and at 67, 66, 66 and 54 ppm for the morpholine carbon atoms (indicating that reaction had occurred at a position in the morpholine ring). High-resolution mass spectra were obtained rather than elemental analysis because of the difficulty in purifying small quantities of semi-solids and gums. The spectra show a molecular ion (M^+), indicating that the photoproducts are isomeric with the N-[2-(morpholin-4-yl)ethyl]-substrates, a base peak for the ion ($\text{C}_5\text{H}_{10}\text{NO}$), and nearly all the spectra show a signal corresponding to the loss of water ($\text{M}^+ - \text{H}_2\text{O}$).

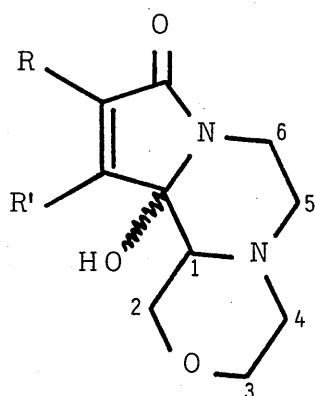
These photoproducts with a new six-membered ring could arise by way of ϵ -hydrogen abstraction to give a biradical which cyclises to form the product. The formation of such a product from the phthalimide substrate is in keeping with similar systems already

reported,¹⁰¹ but this is the first example of an intramolecular photochemical hydrogen transfer/cyclisation in a maleimide substrate. Most other examples of maleimide photochemistry involve reaction of the alkene group, leading to cycloaddition products.³⁰ To reduce the possibility of dimerisation occurring, we irradiated the substrate in more dilute solution (0.005 mol in 400 cm³ acetonitrile, compared with the normal concentration of approximately 0.02 mol in 400 cm³). However, from the reaction mixture we isolated a product (11%) whose spectral data indicate that it is not a cyclised photoproduct. The infrared spectrum shows two carbonyl bands at 1775 and 1705 cm⁻¹, which are typical of the imide carbonyl groups. The ¹³C-nmr spectrum has intense signals at 67.0 and 53.4 ppm indicating that the morpholine ring is intact, and there is no signal for a quaternary carbon atom. From all the spectral data, we can conclude that the alkene group has undergone some form of photoreaction as C=C signals are absent from the spectra. We suspect that simple cycloaddition between two molecules of the maleimide has not taken place, as such a product should give only one signal in the ¹³C-nmr spectrum for four equivalent carbonyl groups, whereas the product isolated gives two carbonyl signals at 175.8 and 174.9 ppm. We postulate that the product could be dimeric, but from the spectral data we cannot determine a structure.

The infrared spectra for both diastereoisomers of (134 a) are very similar. The ^1H -nmr spectra are complex, but both show doublets for the non-equivalent alkene hydrogen atoms at 6.9 and 6.2 ppm, which confirms that the photoproducts are not cycloaddition products. The lower field signals in the ^{13}C -nmr spectra are similar for both diastereoisomers, signals at 167 and 87 ppm for an amide carbonyl and quaternary carbon atom (C-OH) respectively and two signals for non-equivalent alkene carbon atoms at 145 and 129 ppm. The higher field signals show marked differences; the major isomer shows signals which are as expected for the remaining six carbon atoms. The minor isomer, however, gives signals for carbon atoms 2, 3 and 4 at much lower chemical shift values.

	Major Isomer		Minor Isomer
	67.0, 66.9, 66.5	{ 1 2 3 }	66.9 62.6, 60.8 62.6, 60.8
	54.5/53.9	4	44.3
	35.4	5	34.6
	54.5/53.9	6	53.3
	86.5	7	87.1

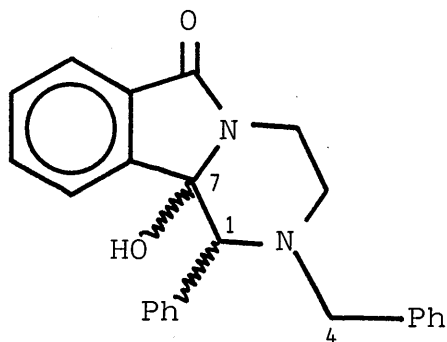
We do not understand why the minor isomer should differ so much from the other in this respect. This result is not an anomaly, however, as we have found that the minor isomers of (134 b and 134 c) also show lower ^{13}C -nmr chemical shift values for the carbon atoms in question. Even more puzzling is the lower chemical shift value for carbon atom-1 in the minor isomers of (134 b and 134 c).



	1	2	3	4
R, R' = $(\text{CH}_2)_4$ Major Isomer	66.7	66.7	66.5	54.3
R, R' = $(\text{CH}_2)_4$ Minor Isomer	61.2	60.0	58.8	43.3
R, R' = $\text{CH}=\text{CHCH}=\text{CH}$ Major Isomer	67.2	66.5	66.2	54.4/54.1
R, R' = $\text{CH}=\text{CHCH}=\text{CH}$ Minor Isomer	62.2	59.3	59.3	43.1

This effect is also seen in the ^{13}C -nmr spectra of the two diastereoisomers of 4-benzyl-2-hydroxy-3-phenyl-4,7-diazatricyclo $[7.4.0.0^{2,7}]$ trideca-9,11,13-trien-8-one (136), the photoproduct from N-(2-dibenzylaminoethyl)phthalimide.¹⁰¹

Major Isomer		Minor Isomer
76.6	1	69.6
52.4	4	43.3
87.0	7	86.9



(136)

We have made models of the photoproducts of (134), and there appears to be no major steric influence in the isomers with the relevant OH and H trans with respect to each other (plate 8).

However, the isomer with the bridgehead OH and H groups cis can be made to adopt a 'cage-like' structure which allows interaction between carbon atoms 2, 3 and 4, and the alkene (or aromatic) and carbonyl groups (plate 9). This could explain the lower chemical shift values for these carbon atoms in the ^{13}C -nmr spectra of the minor isomers. The effect on carbon atom-1 remains a mystery, as it cannot arise by the mechanism mentioned for carbon atoms 2, 3 and 4. The only possibility that we can suggest

PLATE 8

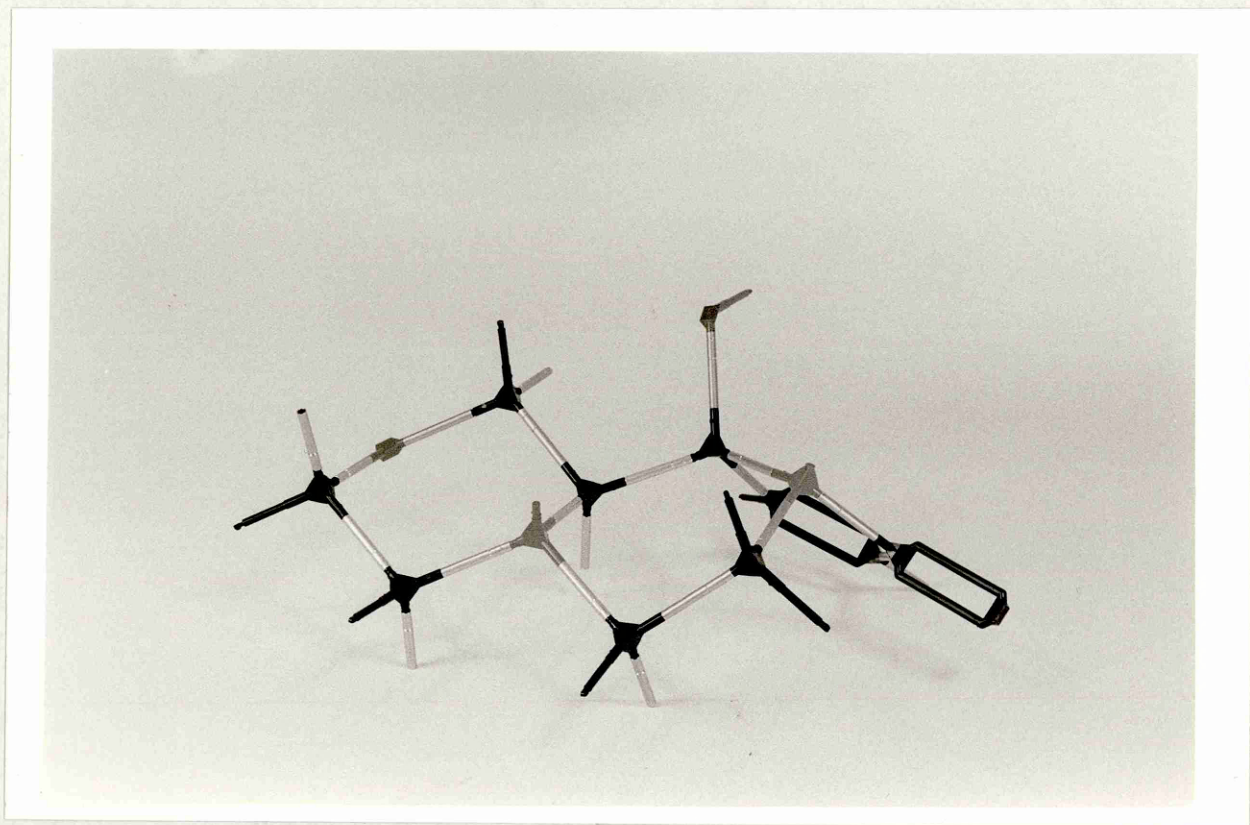
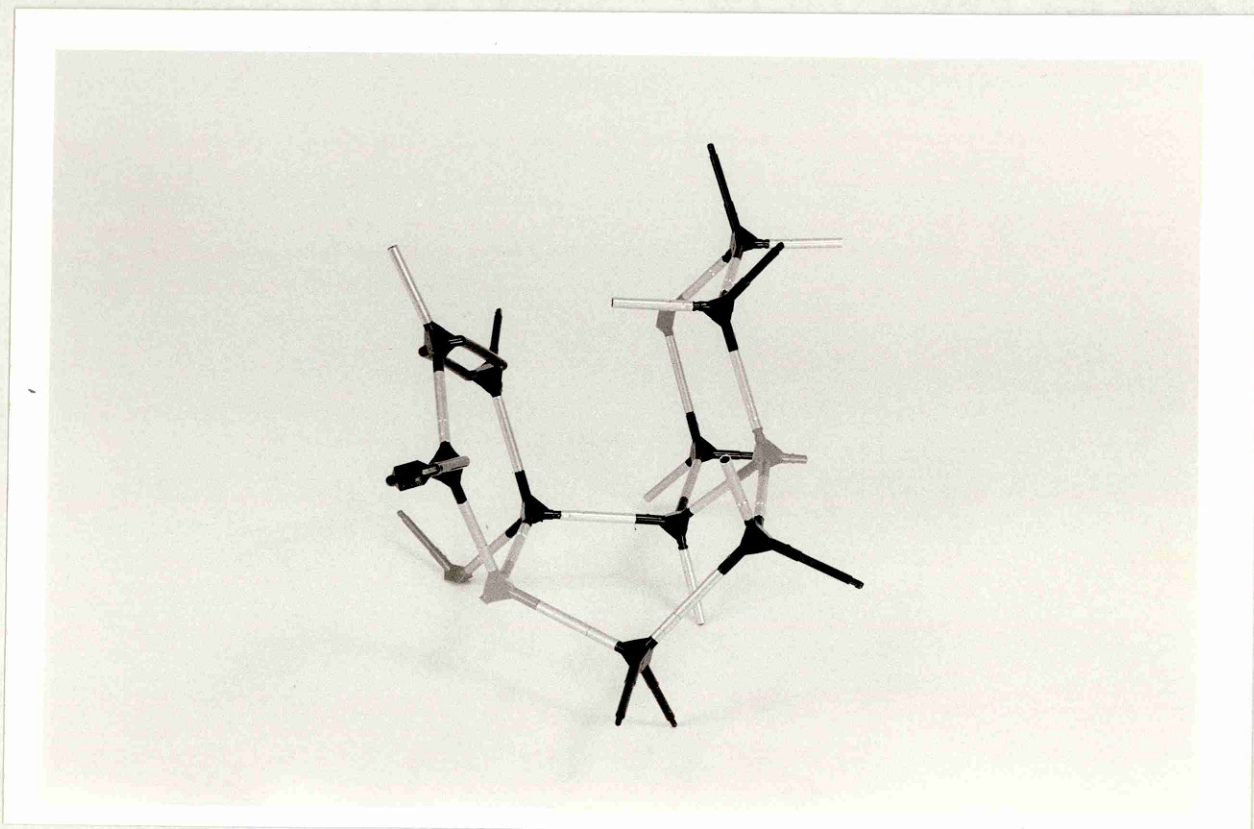
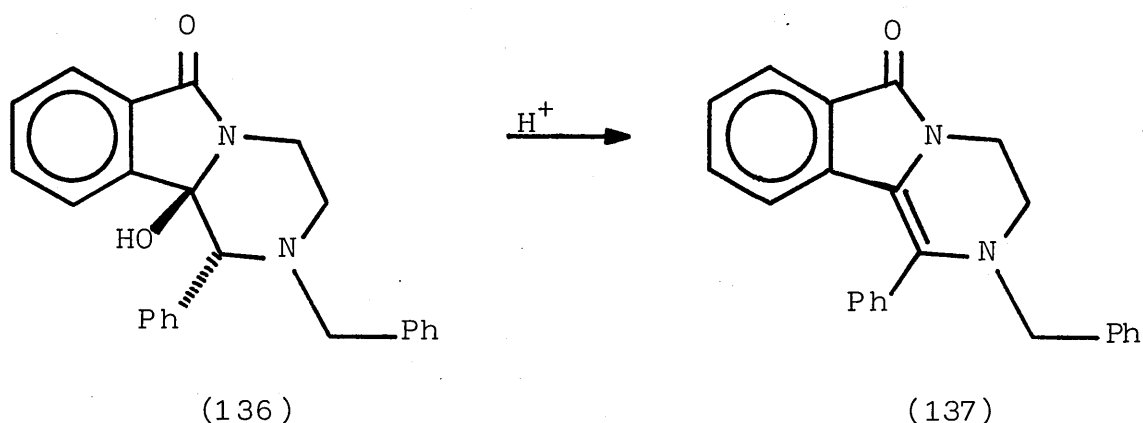


PLATE 9



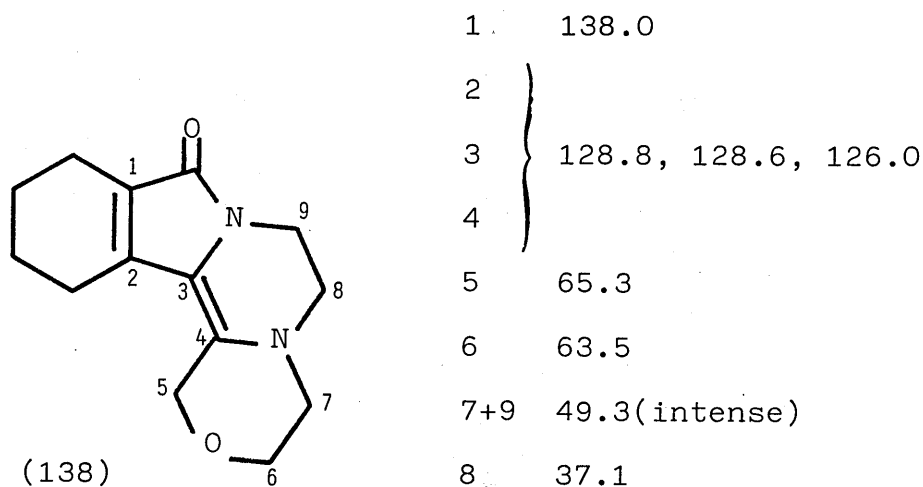
is that the lower chemical shift value is brought about by bond lengthening due to steric compression, but this would be expected also to affect the chemical shift value of the quaternary carbon atom (C-OH), which is found not to be so.

As with the photoproducts from the succinimide substrates, we were interested in the possibility of thermal transformations of some of the unsaturated and aromatic products. A signal in the mass spectra corresponding to the loss of water ($M^+ - H_2O$) suggested that dehydration might be possible, and it had already been shown that (136) readily gave 4-benzyl-3-phenyl-4,7-diazatricyclo[7.4.0.0.^{2,7}]trideca-2(3),9,11,13-tetraen-8-one (137) by acid promoted dehydration.¹⁰¹



A reflux of a mixture of diastereoisomers of (134 c) in aqueous hydrochloric acid gave a complex mixture. Under the same conditions the minor isomer of (134 b) gave what is thought to be a dehydrated product (138), but complete identification was not

possible due to the decomposition of the product. The infrared spectrum shows strong absorption bands at 1720 and 1640 cm^{-1} for the amide carbonyl group and conjugated alkene groups respectively. The ^{13}C -nmr spectrum shows signals at 166.4 ppm for the amide carbonyl carbon atom, 138.0, 128.8, 128.6 and 126.0 ppm for four alkene carbon atoms, and 65.3 and 63.5 ppm for the morpholine carbon atoms adjacent to oxygen. It is significant that there is no signal in the ^{13}C -nmr spectrum corresponding to a quaternary carbon atom (C-OH). An unusual feature of the ^{13}C -nmr data is the chemical shift value (49.3 ppm) for carbon atoms 7 and 9; from molecular models we are unable to suggest why the signals are at lower chemical shift value than expected.



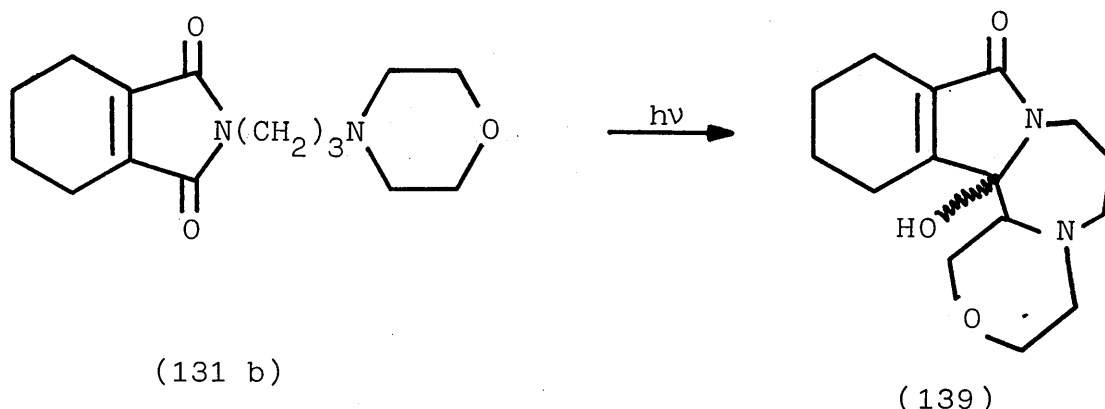
As already indicated, we have attempted to dehydrate some other photoproducts, but without any success, and it is significant that although virtually all the photocyclised products give a signal (usually less than 10% intensity) corresponding to the loss of water in the mass spectra, this signal in the

spectrum of the minor isomer of (134 b) is of 96% intensity. The mass spectral fragmentation is in line with the ready dehydration of this product.

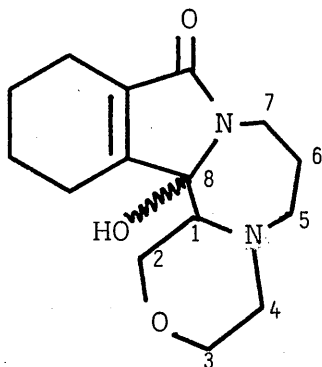
N-[3-(Morpholin-4-yl)propyl]-derivatives

The preparation and spectral characteristics of these substrates have been described in the previous section, and the purpose of these studies was to investigate the possibility of preparing photoproducts with a new perhydro-1,4-diazepine ring.

From the irradiation of tetrahydro-N-[3-(morpholin-4-yl)-propyl]phthalimide (131 b) we have isolated two diastereoisomers of 1-hydroxy-7,11-diaza-4-oxatetracyclo-[9.7.0.0^{2,7}.0^{13,18}]octadec-13(18)-en-12-one (139) in 17% yield (11 + 6%).



The products give the characteristic spectral data for a photocyclised product, and again we have found a major difference between the two diastereoisomers when comparing the ^{13}C -nmr spectra.

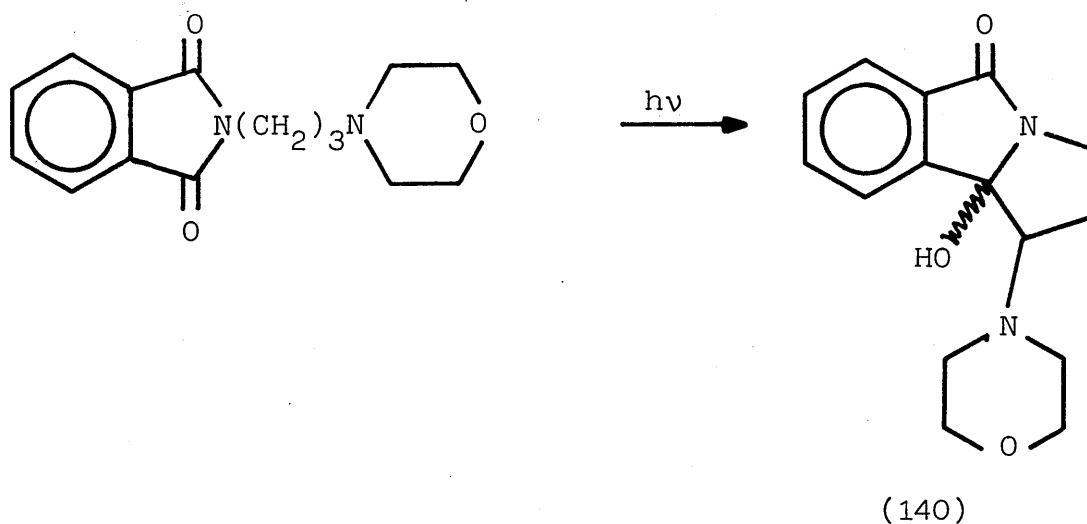


Major Isomer		Minor Isomer
68.5, 66.7, 66.5	$\left. \begin{array}{c} 1 \\ 2 \\ 3 \end{array} \right\}$	63.5, 61.1, 60.1
52.7	4	50.6
39.4	5	41.3
25.3	6	25.4
58.8	7	54.5
92.5	8	90.4

The positions of the signals for carbon atoms 1,2 and 3 show the same effect as do the signals for the corresponding atoms in the photoproducts (134 b and 134 c). A striking feature of the ^{13}C -nmr spectra when comparing the diastereoisomers of the photoproducts from N-[2-(morpholin-4-yl)ethyl] and N-[3-(morpholin-4-yl)propyl]phthalimide and 3,4,5,6-tetrahydrophthalimide is the position of the signals for the carbon atoms 4 and 7.

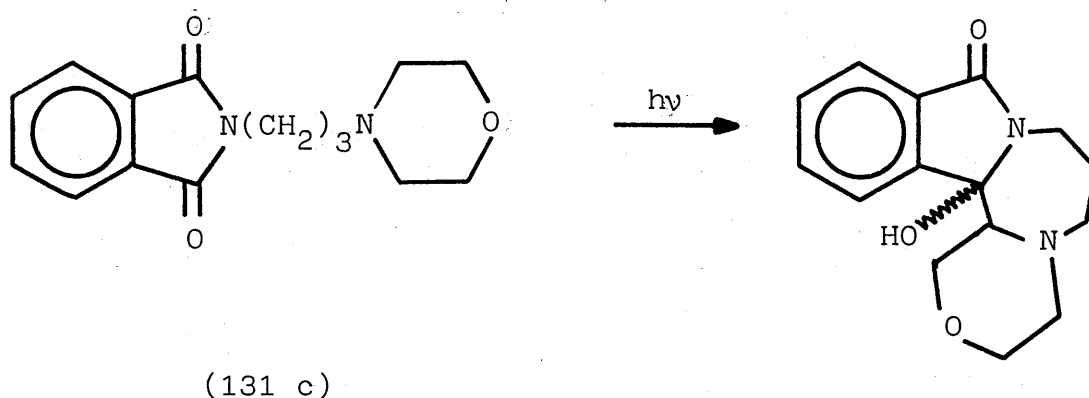
In the previous examples (134) the signals assigned to C-6 and C-4 are near 54 ppm for the major isomer, and 54 and 43 ppm for the minor isomer, but in the above product (139) the signals assigned to C-7 and C-4 are at 58.8 and 52.7 ppm for the major isomer and 54.5 and 50.6 ppm for the minor isomer. It is not possible to compare these ^{13}C -nmr results with those from the analogous saturated systems, as the N-[2-(morpholin-4-yl)ethyl]succinimide and N-[2-(dimethylamino)ethyl]succinimide gave ring expanded products (98 a and 98 b). From N-[3-(morpholin-4-yl)propyl]succinimide only one diastereoisomer was isolated (113) which showed no unexpected effects in its ^{13}C -nmr spectrum, and we have assigned the signals at 57.2 and 51.8 ppm to C-7 and C-4 respectively. (The photoproduct 112, R = H, R' = CH₃, from N-[3-(dimethylamino)propyl]succinimide gave a signal in the ^{13}C -nmr spectrum for C-7 at 58.7 ppm). The major isomer of (139) therefore gives no anomalous results in its ^{13}C -nmr spectrum. The ^{13}C -nmr data for the minor isomer of (139), however, are still puzzling; compared to the major isomer, both C-7 and C-4 give rise to signals in the spectrum at different chemical shift values. Although we cannot be certain which signal arises from C-7 and which from C-4, we note that there is a significant difference in the chemical shift values for the C-4 signals when compared with the ^{13}C -nmr data for the photoproducts derived from N-[2-(morpholin-4-yl)ethyl] and N-[3-(morpholin-4-yl)propyl] substrates.

morpholine hydrogen atoms, which suggests that the morpholine ring is intact. This is also indicated in the ^{13}C -nmr spectrum with intense signals at 67.1 and 52.6 ppm, which are typical for the morpholine carbon atoms. Also present in the ^{13}C -nmr spectrum are signals corresponding to a single carbonyl carbon atom at 170.0 ppm, a quaternary carbon atom (C-OH) at 94.6 ppm, and a tertiary (CH) carbon atom at 69.2 ppm. From these data, we propose that the photocyclised product contains a new five-membered ring, which could arise by way of δ -hydrogen abstraction, and not from ζ -hydrogen abstraction to give a seven-membered ring.



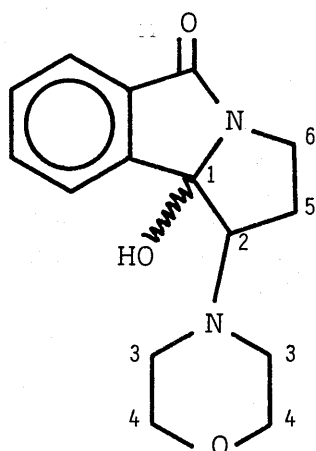
The ^{13}C -nmr spectrum of the first mixture (18%) suggests that a second product is another photocyclised isomer with a new five-membered ring. The chemical shift values from the ^{13}C -nmr spectra of the two diastereoisomers are compared below:

For completeness, we irradiated N-[3-(morpholin-4-yl)-propyl]phthalimide (131 c) in an attempt to isolate two photocyclised diastereoisomers with a new seven-membered ring, which would enable us to investigate the ^{13}C -nmr chemical shift values of carbon atoms 4 and 7 in the two isomers.



Separation of the reaction mixture by silica-gel column chromatography gave five major products, of which three were isolated as mixtures and could not be further separated. ^{13}C -nmr spectra of these mixtures were obtained, and we have attempted to assign the structures of the three products by comparing the spectra.

The first photoproduct (140, 10%) was isolated as a single component, and the infrared spectrum shows a broad absorption band at 3260 cm^{-1} and a strong band at 1680 cm^{-1} for a hydroxyl group and an amide carbonyl group respectively, indicating that a photocyclised product has been formed. The ^1H -nmr spectrum shows strong signals at 3.80 and 2.50 ppm for the



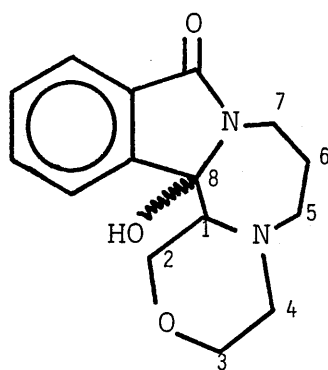
(140)

Pure Isomer

Second Isomer -
component of
mixture

94.6	1	99.3
69.2	2	69.2
67.1(intense)	3	67.0(intense)
52.6(intense)	4	50.6(intense)
29.8	5	28.0
39.4	6	40.7

If the signals for this isomer of (140) are subtracted from the ^{13}C -nmr spectrum for the first mixture, we are left with signals which could correspond to a photocyclised product with a new seven-membered ring (141).

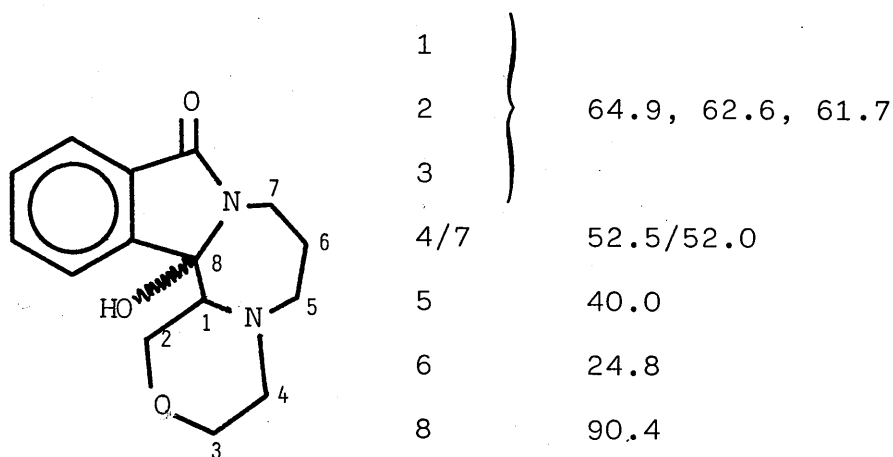


(141)

1	}	68.8, 67.6, 66.4
2		
3		
4		53.3
5		40.2
6		25.4
7		59.2
8		91.7

These chemical shift values are consistent with those obtained for the analogous photoproducts of 3,4,5,6-tetrahydrophthalimide and succinimide derivatives.

The signals for (141) are repeated in the ^{13}C -nmr spectrum for a second mixture (21%), and subtracting them from the spectrum give signals which could correspond to the second photocyclised isomer with a new seven- membered ring.

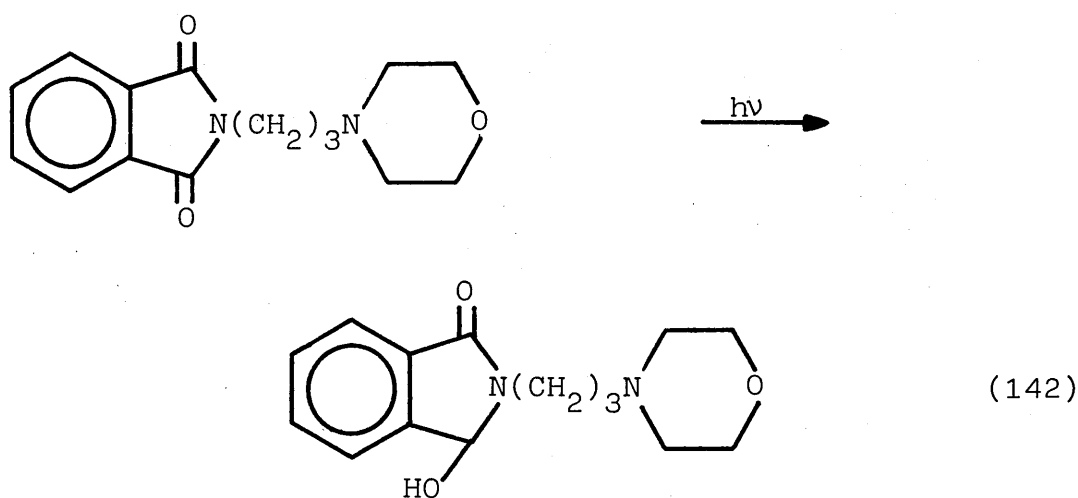


(141)

If our interpretation of the ^{13}C -nmr spectra for the mixtures is correct, the effect for carbon atoms 1,2 and 3 is still noticeable, and we confirm that the chemical shift value for the signal from carbon-4 is not greatly different for the two diastereoisomers of (139) with a seven-membered ring. However, it appears that as the effect on C-4 is lost in going from photoproducts with a piperazine ring to photoproducts with a perhydro-1,4-diazepine ring, C-7 becomes

much more affected. From molecular models of the diastereoisomers of (139 and 141) we cannot suggest why there is a significant chemical shift difference between the isomers for the signal arising from C-7.

The major product isolated from the irradiation of N-[3-(morpholin-4-yl)propyl]phthalimide is a photoreduced compound (142, 32%).



The infrared spectrum show absorption bands at 3330(broad) and 1690 cm^{-1} for a hydroxyl group and a carbonyl group respectively. Although these bands are also characteristic of the photocyclised products, the remaining spectral data do not correspond to such a product. The ^1H -nmr spectrum shows a singlet at 5.76 ppm for one hydrogen atom which is not exchangeable with deuterated water, and the remainder of the spectrum is very similar to that of the starting material. The ^{13}C -nmr spectrum shows signals at 83.2 ppm for a tertiary carbon atom (a doublet by off-resonance) and intense signals at 66.0 and 52.9

ppm for the carbon atoms of an intact morpholine ring. The remainder of the ^{13}C -nmr spectrum is very similar to that of the starting material. The mass spectrum gives a molecular ion at $m/e = 276$, which corresponds to an increase in molecular formula by two hydrogen atoms. This product clearly arises by reaction of the substrate with a hydrogen donor. No good hydrogen donor was added, and acetonitrile (the solvent) is a poor hydrogen donor. The formation of this product in reasonable yield is, therefore, puzzling, and it suggests that for this particular phthalimide substrate, photocyclisation is not as efficient as in other phthalimides. Similarly, the formation of new five- and seven-membered rings is not consistent with previous phthalimide results.

The formation of photocyclised products with a new six-membered ring from N-[2-(morpholin-4-yl)ethyl] substrates of maleimide, 3,4,5,6-tetrahydrophthalimide and phthalimide, indicates that for these unsaturated and aromatic imides there is a preference for cyclisation, which could arise by way of ϵ -hydrogen abstraction. This is in contrast with the corresponding saturated imides which give ring-expanded photoproducts, possibly by way of initial γ -hydrogen abstraction. All three types of N-[3-(morpholin-4-yl)propyl] imide, saturated, unsaturated and aromatic, gave photoproducts in fairly low yields with a new seven-membered ring, which could arise by way of δ -hydrogen abstraction. The fact that the substrates from unsaturated and aromatic imides did not undergo a more efficient

cyclisation process than the saturated analogues to give photoproducts with a new seven-membered ring lends no support to the hypothesis that an electron-transfer mechanism is involved and is more efficient in the unsaturated and aromatic imides. Further work is needed to investigate the mechanism.

Pharmacological Testing

Many of the compounds discussed in chapters 2,3 and 4 have been tested by Reckitt and Colman, Pharmaceutical Division, (Hull), for presynaptic (α_2) and postsynaptic (α_1) agonist and antagonist activity. The tests involved measuring the decrease (α_2 agonist) or increase (α_2 antagonist) in the electrically-induced twitch of vas deferens from mice. α_1 agonists were compared with phenylephrin in their ability to contract the anococcygen muscle from rats and α_1 antagonists reduce the response of the muscle to phenylephrin.

The compounds tested (64 b, c, e and f, 65 b and e, 99, 100, 125 a, 126, 127 a, c and d, 128, 129, 130 a and b) showed no appreciable activity in the above tests.

C H A P T E R F I V E

GENERAL EXPERIMENTAL PROCEDURES

General Procedure for the Preparation of Hydrochloride Salts

After all volatiles were removed in vacuo, an ethereal solution of the residue was dried over anhydrous magnesium sulphate, filtered and saturated with dry hydrogen chloride gas. The resulting precipitate was filtered, washed with dry ether and recrystallised.

The (dialkylamino)alkyl-substituted compound was regenerated by dissolving the hydrochloride salt in a saturated aqueous solution of sodium bicarbonate and extracting three times with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulphate, filtered and the solvent removed in vacuo.

Ultraviolet Irradiation Procedures

Small-scale irradiations were carried out using a Hanovia 125-watt medium-pressure mercury arc, with a quartz water-cooling jacket; the outer vessel containing the reaction solution was of approximately 120 cm³ capacity. Acetonitrile (Rathburn Chemicals) was used as solvent, and nitrogen was bubbled through the solution.

Larger-scale irradiations were carried out using an Applied Photophysics 400-watt medium-pressure mercury arc with a quartz cooling jacket. The capacity of the outer reaction vessel is approximately 400 cm³.

Solvents

'Ether' is diethyl ether, dried over sodium wire, and 'petroleum ether' is the fraction distilling between 40 and 60 °C. The acetonitrile used for irradiations was HPLC grade (Rathburn Chemicals).

Physical Methods

Infrared spectra were recorded on a Pye Unicam SP1050 spectrophotometer, and proton magnetic resonance spectra on a Perkin Elmer R12B 60 MHz, or a Jeol 90 Q 90 MHz Fourier transform spectrometer; the latter was also used for carbon-13 spectra. Medium-field (220 MHz) proton spectra were obtained by courtesy of P.C.M.U., Harwell, on a Perkin Elmer R34 220 MHz continuous wave spectrometer, and high-field (400 MHz) spectra at Warwick University on a Brüker WH 400 MHz Fourier transform spectrometer. Off-resonance carbon-13 nmr spectra were recorded on the Jeol 90 Q 90 MHz instrument, and the frequencies used were 54.33, 54.47, 54.62 and 54.79 KHz. The abbreviations s, d, t and q in the experimental section refer to singlet, doublet, triplet and quartet, respectively. Mass spectra were obtained by courtesy of P.C.M.U., Harwell on a VG Analytical ZAB-IF mass spectrometer or Reckitt and Colman, Pharmaceutical Division (Hull) on a LKB 2091. Microanalytical results were obtained by courtesy of Kent University, Reckitt and Colman

(Hull) or Butterworth Laboratories Ltd.

Chromatographic Techniques

Thin-layer chromatography (T.L.C.) was performed using Camlab polygram silica-gel plates with fluorescent indicator. The T.L.C. plates were visualised by iodine vapour, or by spraying with a solution of 5% ammonium molybdate in 5% concentrated sulphuric acid and then heating to produce a dark blue colour. Column chromatography was carried out using the flash technique^{102, 103}, with silica-gel 60H (Merck) T.L.C. grade as the support, and analar grade solvents as the eluent.

CHAPTER SIX

THE PREPARATION OF SUCCINIMIDE, GLUTARIMIDE,
HYDANTOIN, 5,5-DISUBSTITUTED HYDANTOINS, DIHYDRO-
URACIL, MALEIMIDE AND PHTHALIMIDE SUBSTRATES

SUCCINIMIDE MANNICH BASES

General Method

Succinimide (9.9 g, 0.10 mol), formaldehyde (7.5 g, 40% w/v in water, 0.090 mol) and secondary amine (0.10 mol) were added to ethanol (10 cm³) and heated on a water bath for 10 mins. The solution was cooled overnight and then filtered to obtain the crude product.

(a) N-(Morpholin-4-ylmethyl)succinimide (62 a)

The product was recrystallised from ethanol to give a white solid (14.5 g, 81%). mp: 112-114 °C (lit.⁷¹ 111 °C). ir(Nujol) $\bar{\nu}$ /cm⁻¹: 1770(w), 1700(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 4.42(s, 2H); 3.85 - 3.55 (m, 4H); 2.75(s, 4H); 2.70 - 2.50(m, 4H).

(b) N-(Piperidin-1-ylmethyl)succinimide (62 b)

The product was recrystallised from ethanol to give a white solid (13.5 g, 77%). mp: 109 - 111 °C (lit.⁷⁰ 106 - 107 °C). ir(Nujol) $\bar{\nu}$ /cm⁻¹: 1775(w), 1700(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 4.40(s, 2H); 2.72(s, 4H); 2.60 - 2.40(m, 4H); 1.90 - 1.30 (m, 6H).

(c) N-(Diallylaminomethyl)succinimide (62 c)

After cooling overnight the product did not crystallise. The volatiles were removed in vacuo to leave a straw-coloured viscous oil, which was purified by silica-gel

column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform. One major band was collected and evaporated to give a colourless oil (13.35 g, 72%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3090(w), 1710(s), 1645(shoulder). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 6.20 - 5.55(m, 2H); 5.30 - 4.95(m, 4H); 4.41(s, 2H); 3.32(d, J=6 Hz, 4H); 2.71(s, 4H). Found: C, 63.76; H, 7.65; N, 13.32; $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$ requires: C, 63.44; H, 7.74; N, 13.45%.

(d) N-(Diethylaminomethyl)succinimide (62 d)

After cooling overnight, the product did not crystallise, so a hydrochloride salt was made as described under the general procedure for the preparation of hydrochloride salts. The hydrochloride salt was recrystallised from propan-2-ol to give a white solid (12.4 g, 62%). mp: 142 - 144.5 $^{\circ}\text{C}$. Neutralisation, and evaporation of the dichloromethane extract gave a colourless oil (9.6 g, 58%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1775(w), 1710(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 4.45(s, 2H); 2.73(s, 4H); 2.63(q, J=7 Hz, 4H); 1.08(t, J=7 Hz, 6H). Found: C, 58.61; H, 8.89; N, 15.29; $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 58.67; H, 8.75; N, 15.20%.

(e) N-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)succinimide (62 e)

The product was recrystallised from ethanol to give a white solid (8.2 g, 47%). mp: 73 - 75 $^{\circ}\text{C}$. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3080(w), 1770(w), 1700(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3)

δ /ppm: 5.63(s, 2H); 4.45(s, 2H); 3.25 - 2.95(m, 2H); 2.85 - 2.55(m, 6H); 2.30 - 1.90(m, 2H). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 178.1, 125.1, 124.9, 60.0, 49.7, 48.0, 28.2(intense), 26.1. Found: C, 61.66; H, 7.00; N, 14.23; $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 61.84; H, 7.27; N, 14.42%.

(f) N-(1,2,3,4-Tetrahydroisoquinolin-2-yl-methyl)-succinimide (62 f)

The product was recrystallised from ethanol to give a white solid (15.6 g, 71%). mp: 122 - 124 $^{\circ}\text{C}$. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1775(w), 1710(s). ^1H -nmr(60 MHz, CDCl_3) δ /ppm: 7.10(s, 4H); 4.62(s, 2H); 3.80(s, 2H); 2.91(s, 4H); 2.72(s, 4H). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 178.1, 134.5, 134.2, 128.8, 126.7, 126.2, 125.7, 60.0, 52.9, 49.0, 29.3, 28.2(intense).

(g) N-(Dibenzylaminomethyl)succinimide (62 g)

The product was recrystallised from ethanol to give a white solid (16.9 g, 61%). mp: 122 - 124 $^{\circ}\text{C}$. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1770(w), 1700(s). ^1H -nmr(60 MHz, CDCl_3) δ /ppm: 7.38(s, 10H); 4.55(s, 2H); 3.78(s, 4H); 2.52(s, 4H). Found: C, 73.77; H, 6.70; N, 9.01; $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$ requires: C, 74.00; H, 6.54; N, 9.08%.

(h) N-(Benzylmethylaminomethyl)succinimide (62 h)

The product was recrystallised from ethanol to give a white solid (15.1 g, 72%). mp: 70 - 72 $^{\circ}\text{C}$. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1765(w), 1695(s). ^1H -nmr(60 MHz, CDCl_3) δ /ppm:

7.32(s, 5H); 4.55(s, 2H); 3.70(s, 2H); 2.70(s, 4H);
2.27(s, 3H). Found: C, 67.20; H, 7.20; N, 11.96; $C_{13}H_{16}N_2O_2$
requires: C, 67.22; H, 6.94; N, 12.06%.

(i) N-(Dimethylaminomethyl)succinimide (62 i)

After cooling overnight, the product did not crystallise, so a hydrochloride salt was made as described under the general procedure for the preparation of hydrochloride salts. The hydrochloride salt was recrystallised from ethanol to give a white solid (11.7 g, 68%). mp: 145 - 148 °C. Neutralisation and evaporation of the dichloromethane extract gave a colourless oil (9.1 g, 65%).
ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1775(w), 1720(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 4.37(s, 2H); 2.76(s, 4H); 2.32(s, 6H). Found: C, 53.88; H, 8.06; N, 17.89; $C_7H_{12}N_2O_2$ requires: C, 53.83; H, 7.75; N, 17.94%.

(j) 2-Phenylsuccinimide

2-Phenylsuccinimide was prepared by the method described by Wegscheider and Hecht.¹⁰⁴

(k) N-(Morpholin-4-ylmethyl)-2-phenylsuccinimide

This compound was made from 2-phenylsuccinimide using the same general procedure as for succinimide. The product was recrystallised from ethanol to give a white solid (17.0 g, 69%). mp: 113 - 115 °C. (lit.¹⁰⁵ 111 - 112 °C.) ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1775(w), 1700(s), 1600(w). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.40 - 7.15(m,

5H); 4.49(s, 2H); 4.02(dd, J=9 and 5 Hz, 1H); 3.85 - 3.55(m, 4H); 3.21(dd, J=18½ and 9 Hz, 1H); 2.81(dd, J=18½ and 5 Hz, 1H); 2.70 - 2.50(m, 4H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm: 178.6, 176.9, 137.2, 129.2, 128.0, 127.3, 66.8(intense), 60.4, 51.0(intense), 46.0(d), 36.9(t).

(1) N-(Dimethylaminomethyl)-2-phenylsuccinimide

This compound was made from 2-phenylsuccinimide using the same general procedure as for succinimide. The product was recrystallised from ethanol to give a white solid (14.2 g, 68%). mp: 96 - 98 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1770(w-m), 1695(s), 1600(w). ¹H-nmr(60 MHz, CDCl₃) δ/ppm: 7.35 - 7.20(m, 5H); 4.45(s, 2H); 4.05(dd, J=9 and 5 Hz, 1H); 3.25 (dd, J=18½ and 9 Hz, 1H); 2.84(dd, J=18½ and 5 Hz, 1H); 2.33 (s, 6H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm: 178.6, 177.0, 137.3, 129.3, 128.0, 127.3, 61.2, 46.0(d), 43.1(intense, q), 37.1(t). Found; C, 66.99; H, 7.04; N, 12.12; C₁₃H₁₆N₂O₂ requires C, 67.22; H, 6.94, N, 12.06%.

GLUTARIMIDE MANNICH BASES

General Method

Formaldehyde (15.0 g, 40% w/v in water, 0.180 mol) and secondary amine (0.20 mol) were mixed together. The glutarimide (0.10 mol) was added, and the mixture warmed until a solution formed. After cooling a solid was obtained by filtration.

Bis-(1,2,3,4-tetrahydroisoquinolin-2-yl)methane (63)

The product was recrystallised from ethanol to give a white solid. mp: 87 - 89 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1605(w), 740(m-s), 735(m-s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.09 (narrow m, 8H); 3.74(s, 4H); 3.27(s, 2H); 2.87(s, 8H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 135.1, 134.8, 128.7, 126.7, 126.0, 125.5, 80.7, 54.4(intense), 49.1(intense), 29.1(intense).

(a) N-(Morpholin-4-ylmethyl)glutarimide (64 a)

The product was recrystallised from ether/ethanol to give a white solid (8.9 g, 42%). mp: 103.5 - 106.5 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1726(m), 1668(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 4.75(s, 2H); 3.90 - 3.55(m, 4H); 2.85 - 2.40(m, 8H); 2.16 - 1.75(m, 2H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 173.4, 67.0(intense), 60.0, 51.4(intense), 33.0(intense), 17.1. Found: C, 56.23; H, 7.36; N, 13.14; $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_3$ requires: C, 56.59; H, 7.60; N, 13.20%.

(b) N-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)-glutarimide (64 b)

The product was recrystallised from ether/ethanol to give a white solid (17.3 g, 67%). mp: 93 - 95 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1735(w), 1686(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.08(s, 4H); 4.96(s, 2H); 3.84(s, 2H); 2.50 - 3.00(m, 8H); 2.20 - 1.85(m, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 173.4, 134.8, 133.9, 128.6, 126.6, 126.0, 125.5, 59.8, 53.2, 49.1, 32.9(intense), 29.1, 17.0. Found: C, 70.09; H, 7.15; N, 10.86; C₁₅H₁₈N₂O₂ requires: C, 69.74; H, 7.02; N, 10.84%.

(c) N-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)glutarimide (64 c)

The product was recrystallised from ether to give a white solid (12.7 g, 61%). mp: 71 - 74 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3029(w), 1720(w), 1684(s), ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 5.70(s, 2H); 4.86(s, 2H); 3.30 - 3.05(m, 2H); 2.90 - 2.55(m, 6H); 2.40 - 1.85(m, 4H). Found: C, 63.39; H, 7.85; N, 13.41; C₁₁H₁₆N₂O₂ requires C, 63.44; H, 7.74; N, 13.45%.

(d) N-(Piperidin-1-ylmethyl)glutarimide (64 d)

The product was recrystallised from ether/petroleum ether to give a white solid (10.3 g, 49%). mp: 83 - 85 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1726(m), 1667(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 4.73(s, 2H); 2.90 - 2.30(m, 8H); 2.20 - 1.20(m, 8H). Found: C, 62.56; H, 8.53; N, 13.22;

$C_{11}H_{18}N_2O_2$ requires: C, 62.84; H, 8.63; N, 13.32%.

(e) 3,3-Dimethyl-N-(morpholin-4-ylmethyl)glutarimide
(64 e)

The product was recrystallised from ether/ethanol to give a white solid (11.3 g, 47%). mp: 99 - 101 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1721(m), 1678(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 4.74(s, 2H); 3.80 - 3.55(m, 4H); 2.75 - 2.50(m, 8H); 1.11(s, 6H). Found: C, 59.99; H, 8.62; N, 11.72; $C_{12}H_{20}N_2O_3$ requires C, 59.98; H, 8.39; N, 11.66%.

(f) 3,3-Dimethyl-N-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)glutarimide (64 f)

The product was recrystallised from ether/ethanol to give a white solid (17.4 g, 61%). mp: 72 - 74 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1725(m), 1679(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 7.04(s, 4H); 4.94(s, 2H); 3.80(s, 2H); 2.90(s, 4H); 2.51(s, 4H); 1.07(s, 6H). Found: C, 71.09; H, 7.64; N, 9.69; $C_{17}H_{22}N_2O_2$ requires C, 71.30; H, 7.74; N, 9.78%.

(g) 3,3-Dimethyl-N-(1,2,5,6-tetrahydropyridin-1-ylmethyl)-glutarimide (64 g)

The product was recrystallised from ether to give a white solid (13.5 g, 57%). mp: 60 - 62 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3030(w), 1720(m), 1680(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 5.65(s, 2H); 4.84(s, 2H); 3.25 - 3.00(m, 2H); 2.76(t, J=5 Hz, 2H); 2.51(s, 4H); 2.30 - 1.90(m, 2H);

1.10(s, 6H). Found: C,66.31; H,8.39; N,11.82; $C_{13}H_{20}N_2O_2$ requires: C,66.07; H,8.53; N,11.85%.

(h) 3,3-Dimethyl-N-(piperidin-1-ylmethyl)glutarimide
(64 h)

The product was recrystallised from ether/petroleum ether to give a white solid (12.1 g, 51%). mp: 86 - 88 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1724(m), 1680(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 4.77(s, 2H); 2.53(s, 8H); 2.15 - 1.15(m, 6H); 1.11(s, 6H). Found: C,65.70; H,9.10; N,11.70; $C_{13}H_{22}N_2O_2$ requires: C,65.52; H, 9.30; N, 11.57%.

PYRROLIDIN-2-ONE MANNICH BASES

General Method

Formaldehyde (15.0 g, 40% w/v in water, 0.180 mol) and secondary amine (0.20 mol) were mixed together. Pyrrolidin-2-one (0.10 mol) was added and the mixture warmed on a water bath for 30 minutes. After cooling all volatiles were removed in vacuo and a hydrochloride salt was prepared as described under the general procedure for the preparation of hydrochloride salts.

(a) N-(Morpholin-4-ylmethyl)pyrrolidin-2-one (86)

The hydrochloride salt was recrystallised from ethanol to give a white solid (14.5 g, 66%). mp: 173 - 175 °C. The neutralised product was recrystallised from ether (10.1 g, 55%). mp: 67 - 69 °C, (lit.⁸² 68.5 - 69.5 °C). ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1680(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 3.95(s, 2H); 3.80 - 3.35(m, 6H); 2.70 - 1.70(m, 8H).

(b) N-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)pyrrolidin-2-one (87)

The hydrochloride salt was recrystallised from ethanol to give a white solid (16.1 g, 74%). mp: 163 - 165 °C. Neutralisation of the salt gave a colourless oil (11.4 g, 63%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3033(w), 1680(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 5.71(s, 2H); 4.05(s,

2H); 3.51(t, J=6 Hz, 2H); 3.03(s, 2H); 2.80 - 1.70(m, 8H). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 175.6, 125.0(intense), 64.3, 49.9, 47.7, 47.6, 31.2, 26.0, 18.1. Found: C, 66.42; H, 9.10; N, 15.51; $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$ requires: C, 66.63; H, 8.95; N, 15.54%.

(c) N-(Dimethylaminomethyl)pyrrolidin-2-one (90)

The hydrochloride salt was recrystallised from ethanol to give a white solid (10.9 g, 61%). mp: 161 - 163.5 $^{\circ}\text{C}$. Neutralisation of the salt gave a colourless oil (6.8 g, 48%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1695(s). ^1H -nmr(60 MHz, CDCl_3) δ /ppm: 3.89(s, 2H); 3.49(t, J=7 Hz, 2H); 2.50 - 2.00(m, 10H, including strong singlet at 2.26). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 175.8, 65.4, 47.6, 42.7(intense), 31.2, 18.2.

N-METHYL-2-PHENYLSUCCINIMIDE MANNICH BASES

N-Methyl-2-phenylsuccinimide

2-Phenylsuccinic acid (19.4 g, 0.10 mol) was added in small portions to methylamine solution (41 cm³, 30% w/v in water, 0.40 mol) in water (100 cm³) and the mixture heated on a water bath until it had evaporated to dryness. The residue was heated to 210 °C. On cooling, the solid was recrystallised from ethanol (and decolourised with activated charcoal) to give a white solid (14.9 g, 79%). mp: 70 - 72 °C, (lit.⁷⁷ 71 - 73 °C). ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1772(w), 1698(s), 1608(w). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.45 - 7.15(m, 5H); 4.03(dd, J=9 and 5 Hz, 1H); 3.25(dd, J=18 and 9 Hz, 1H); 3.05(s, 3H); 2.80(dd, J= 18 and 5 Hz, 1H).

General Method

Formaldehyde (0.75 g, 40% w/v in water, 0.0090 mol), N-methyl-2- phenylsuccinimide (1.89 g, 0.010 mol) and secondary amine (0.010 mol) were mixed in toluene (10 cm³) and refluxed for 24 hours. After cooling all volatiles were removed in vacuo, and a hydrochloride salt was prepared as described under the general procedure for the preparation of hydrochloride salts.

(a) N-Methyl-2-phenyl-2-(piperidin-1-ylmethyl)succinimide
(95 a)

The hydrochloride salt was recrystallised from propan-2-ol

to give a white solid (2.0 g, 69%), mp: 188 - 190 °C, (lit.⁷⁹ 188 - 189 °C). The neutralised product was recrystallised from ethanol, to give a white solid (1.60 g, 62%). mp: 82.5 - 84.5 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1775(m), 1693(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.40 - 7.10(m, 5H); 3.35 - 2.20(m, 11H, including strong singlet at 3.01); 1.60 - 1.20(m, 6H).

(b) N-Methyl-2-(morpholin-4-ylmethyl)-2-phenylsuccinimide
(95 b)

The hydrochloride salt was recrystallised from ethanol to give a white solid (1.2 g, 41%). mp: 179 - 181 °C, (lit.⁷⁹ 178 - 182 °C). The neutralised product was recrystallised from ethanol to give a white solid (0.81 g, 31%). mp: 132 - 134 °C, (lit. 131 - 133 °C). ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1770(m), 1690(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.60 - 7.25(m, 5H); 3.75 - 3.50(m, 4H); 3.30 - 3.00(m, 5H, including strong singlet at 3.05); 2.75 - 2.40(m, 6H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 180.0, 175.9, 139.4, 128.9, 127.7, 126.5, 67.2 (intense), 66.7, 55.5(intense), 53.6, 39.9, 24.8.
Found: C, 66.47; H, 6.77; N, 9.68; C₁₆H₂₀N₂O₃ requires: C, 66.65; H, 6.99; N, 9.72%.

(c) N-Methyl-2-phenyl-2-(1,2,5,6-tetrahydropyridin-1-ylmethyl)succinimide (95 c)

The hydrochloride salt was recrystallised from propan-2-ol to give a white solid (1.9 g, 66%). mp: 177- 179 °C.

The neutralised product was recrystallised from ethanol to give a white solid (1.5 g, 59%). mp: 63 - 65 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3035(w), 1774(m), 1700(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.60 - 7.20(m, 5H); 5.63(s, 2H); 3.45 - 2.55(m, 11H, including strong singlet at 3.03); 2.25- 1.80(m, 2H). Found: C, 71.59; H, 7.21; N, 9.68; $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$ requires: C, 71.81; H, 7.09; N, 9.85%.

(d) 2-(Diethylaminomethyl)-N-methyl-2-phenyl-succinimide
(9.5 d)

The hydrochloride salt was recrystallised from ethanol to give a white solid (2.2 g, 79%). mp: 180 - 182 °C (lit.⁷⁹ 181 - 183 °C). Neutralisation of the salt gave a colourless oil (1.7 g, 69%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1776(m), 1705(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.80 - 7.20(m, 5H); 3.55 - 2.35(m, 11H, including a strong singlet at 3.01, and a quartet, $J=7$ Hz, at 2.53); 0.91(t, $J=7$ Hz, 6H).

OTHER N-(DIALKYLAMINOALKYL)IMIDES

General Methods

(a) Imide (0.10 mol), N-(2-chloroethyl)amine (0.10 mol) and anhydrous sodium carbonate (5.3 g, 0.050 mol) were mixed together and heated at 160 - 180 °C for two hours. After cooling, ethanol and activated charcoal were added and the mixture was heated, filtered and cooled. The resulting solid was filtered and recrystallised. If the product did not crystallise, a hydrochloride salt was made as described under the general procedure for the preparation of hydrochloride salts, or the product was purified by column chromatography.

(b) Anhydride (0.10 mol) and N-(2-aminoalkyl)amine (0.10 mol) were mixed together and heated at 180 °C for 3 hours. The work-up procedures were the same as in (a) above.

(c) (i) Imide (0.10 mol), dibromoalkane (0.20 mol) and anhydrous sodium carbonate (5.3 g, 0.050 mol) were mixed together and heated at 150 °C for 2 hours. After cooling, the mixture was washed with large quantities of hexane or petroleum ether to remove the excess of dibromoalkane. The residue was dissolved in ethyl acetate, filtered and extracted with water to remove any imide. The ethyl acetate layer was dried over anhydrous magnesium sulphate, filtered and the solvent removed.

(ii) N-(Bromoalkyl)imide (0.050 mol), secondary amine (0.050 mol) and triethylamine (5.1 g, 0.050 mol) were mixed together in dimethylformamide (10 cm³) and heated at 100 °C for 2 hours. For amines used in aqueous solutions, the cold reaction mixture was neutralised with sodium bicarbonate, extracted with dichloromethane, dried over anhydrous magnesium sulphate, filtered, and the volatiles removed in vacuo.

For other amines, the triethylammonium bromide salt was filtered and washed with dimethylformamide. All volatiles were removed from the combined dimethylformamide solutions in vacuo. The resulting residue was purified by column chromatography, or a hydrochloride salt was prepared as described under the general procedure for the preparation of hydrochloride salts.

Succinimide

(a) N-[2-(Morpholin-4-yl)ethyl] succinimide (98 a)

General method (b) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 15% methanol/85% chloroform. One major band was collected and evaporated to give a colourless oil which solidified on standing, (12.3 g, 58%). mp: 79 - 81 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 1770(w), 1700(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 3.85 - 3.50(m, 6H); 2.85 - 2.35(m, 10H, including strong singlet at 2.72). Found: C, 56.49, H, 7.72; N, 13.09;

$C_{10}H_{16}N_2O_3$ requires: C,56.59; H,7.60; N,13.20%.

(b) N-[2-(Dimethylamino)ethyl] succinimide (98 b)

General method (b) was employed.

A hydrochloride salt of the product was prepared and recrystallised from ethanol to give a white solid (14.2 g, 69%). mp: 196 - 198 °C. Neutralisation and evaporation of the dichloromethane extract gave a colourless oil, (8.7 g, 51%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(w), 1700(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 3.64(t, J=7 Hz, 2H); 2.72(s, 4H); 2.51(t, J=7 Hz, 2H); 2.25(s, 6H). ^{13}C -nmr(90 MHz, HCl salt, D_2O) δ/ppm : 183.5, 57.2, 45.6(intense, q), 36.2(t), 30.8(intense, t). Found: C,56.31; H,8.49; N,16.48; $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$ requires: C,56.45; H,8.30; N,16.46%.

(c) N-[3-(Morpholin-4-yl)propyl] succinimide
(98 c)

General method (b) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a colourless oil, which solidified on standing (17.6 g, 78%). mp: 65.5 - 67.5 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1760(w), 1690(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 3.50 - 3.85(m, 6H); 2.73(s, 4H); 2.25 - 2.57(m, 6H); 1.74(quintet, J=8 Hz, 2H). ^{13}C -nmr(90 MHz, CDCl_3) δ

/ppm: 177.2, 67.0(intense), 56.3, 53.6(intense), 37.2, 28.2(intense), 24.3. Found: C, 58.51; H, 7.91; N, 12.39; $C_{11}H_{18}N_2O_3$ requires: C, 58.39, H, 8.02; N, 12.38%.

(d) N-[3-(Dimethylamino)propyl] succinimide
(98 d)

General method (b) was employed.

A hydrochloride salt of the product was prepared and recrystallised from ethanol to give a white solid (19.4 g, 88%). mp: 193 - 195 °C. Neutralisation and evaporation of the dichloromethane extract gave a colourless oil (13.2 g, 72%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(w), 1700(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 3.57(t, J=7 Hz, 2H); 2.69(s, 4H); 2.45 - 1.50(m, 10H, including strong singlet at 2.19). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 177.2, 57.0, 45.4(intense, q), 37.2(t), 28.1(intense), 25.7. Found: C, 58.59; H, 8.79; N, 15.30; $C_9H_{16}N_2O_2$ requires: C, 58.67; H, 8.75; N, 15.21%.

(e) N-[4-(Morpholin-4-yl)butyl] succinimide
(101 a)

General method (c) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a pale yellow oil (13.4 g, 56%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1772(w), 1700(s). $^1\text{H-nmr}$ (60

MHz, CDCl_3) δ /ppm: 3.75 3.65(m, 4H); 3.53(t, J=7 Hz, 2H); 2.70(s, 4H); 2.45 - 2.24(m, 6H); 1.60 - 1.50(m, 4H). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 177.2, 66.9(intense), 58.3, 53.7(intense), 38.6, 28.1(intense), 25.6, 23.8.
Found: C, 59.87; H, 8.27; N, 11.59; $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_3$ requires: C, 60.00; H, 8.39; N, 11.66%.

(f) N-[4-(Dimethylamino)butyl] succinimide
(101 b)

General method (c) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a pale yellow oil (13.1 g, 66%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(w), 1700(s). ^1H -nmr(60 MHz, CDCl_3) δ /ppm: 3.54(t, J=7 Hz, 2H); 2.72(s, 4H); 2.65 - 2.25(m, 8H, including strong singlet at 2.31); 1.80 - 1.40(m, 4H). Mass Spectrum: $m/e = 198(\text{M}^+)$, 58(base, $\text{C}_3\text{H}_8\text{N}$).

(g) N-[5-(Dimethylamino)pentyl] succinimide
(101 c)

General method (c) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a pale yellow oil (11.9 g,

56%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(w) 1700(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 3.50(t, J=7 Hz, 2H); 2.70(s, 4H); 2.45 - 2.20(m, 8H, including strong singlet at 2.21); 1.80 - 1.35(m, 6H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 177.2, 59.6, 45.4(intense), 38.7, 28.1(intense), 27.6, 27.2, 24.7. Mass Spectrum: $m/e = 212(\text{M}^+)$, 58(base, $\text{C}_3\text{H}_8\text{N}$).

(h) N-[6-(Dimethylamino)hexyl] succinimide (101 d)

General method (c) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a pale yellow oil(11.8 g, 52%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(w), 1700(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 3.49(t, J=7 Hz, 2H); 2.68(s, 4H); 2.40 - 2.15(m, 8H, including strong singlet at 2.27); 1.80 - 1.15(m, 8H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 177.1, 59.3, 45.1(intense), 38.5, 28.0(intense), 27.4, 27.0, 26.7, 26.5. Mass Spectrum: $m/e = 226(\text{M}^+)$, 58(base, $\text{C}_3\text{H}_8\text{N}$).

Glutarimide

N-[2-(Morpholin-4-yl)ethyl] glutarimide (99)

General method (a) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform. One major band was collected and evaporated to give a pale yellow oil(11.8 g, 52%).

graphy using an eluent ranging from chloroform to 15% methanol/85% chloroform. One major band was collected and evaporated to give a colourless oil which solidified on standing (16.3 g, 72%). mp: 80 - 82 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1721(m), 1667(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 3.92(t, J=7 Hz, 2H); 3.70 - 3.60(m, 4H); 2.75 - 2.40(m, 10H); 1.93(quintet, J=6 Hz, 2H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 172.4, 67.0(intense), 55.9, 53.7(intense), 36.3(intense), 32.8, 17.2. Found: C, 58.17; H, 7.89; N, 12.29; $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$ requires: C, 58.39; H, 8.02; N, 12.38%.

1,2,3,6-Tetrahydrophthalimide

1,2,3,6-Tetrahydro-N- 2-(morpholin-4-yl)ethyl phthalimide
(100)

General method (a) was employed.

The product was purified by silica-gel column chromatography using an eluent ranging from chloroform to 8% methanol/92% chloroform. One major band was collected and evaporated to give a straw-coloured oil (16.6 g, 63%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3042(w), 1772(w), 1709(s), 1645(shoulder). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 6.00 - 5.80(m, 2H); 3.85 - 3.45(m, 6H); 3.20 - 3.00(m, 2H); 2.65 - 2.25(m, 10H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 180.0, 127.6 (intense), 67.0(intense), 55.1, 53.4(intense), 39.0(intense), 35.7, 23.5(intense). Found: C, 63.57; H, 7.71; N, 10.51; $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ requires: C, 63.62; H, 7.63; N, 10.60%.

Maleimide

N-[2-(Morpholin-4-yl)ethyl] maleimide (132 a)

Maleimide (9.7 g, 0.10 mol), N-(2-chloroethyl)morpholine (14.9 g, 0.10 mol) and anhydrous sodium carbonate (5.3 g, 0.050 mol) were mixed together and heated at 120 °C for 45 minutes. After cooling the reaction mixture was washed with chloroform. The chloroform extracts were dried over anhydrous magnesium sulphate, filtered, and the solvent removed. The resulting residue was purified by silica-gel column chromatography using an eluent ranging from chloroform to 10% acetone/90% chloroform. One major band was collected and evaporated to give a pale yellow semi-solid (6.5 g, 31%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3095(w), 1768(w), 1710(s), 1678(shoulder). ¹H-nmr(60 MHz, CDCl_3) δ/ppm : 6.71(s, 2H); 3.85 - 3.45(m, 6H); 2.70 - 2.35(m, 6H). ¹³C-nmr(90 MHz, CDCl_3) δ/ppm : 170.7, 134.1 (intense), 66.9(intense), 55.9, 53.4(intense), 34.8. Found: C, 56.89; H, 6.58; N, 13.21; $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 57.13; H, 6.71; N, 13.33%.

3,4,5,6-Tetrahydrophthalimide

(a) 3,4,5,6-Tetrahydro-N-[2-(morpholin-4-yl)ethyl]-phthalimide (131 a)

General method (b) was employed.

The hydrochloride salt of the product was prepared and recrystallised from ethanol to give a white solid

(21.6 g, 72%). mp: 226.5 - 228.5 °C. Neutralisation and evaporation of the dichloromethane extract gave a straw-coloured oil (16.1 g, 61%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1765(m), 1710(s), 1676 (shoulder). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 3.85 - 3.45(m, 6H); 2.75 - 2.25(m, 10H); 1.95 - 1.60(m, 4H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 171.0, 141.4(intense), 66.9(intense), 56.4, 53.5(intense), 34.5, 21.4(intense), 19.9(intense). Found: C,63.39; H,7.80; N,10.68; $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ requires: C,63.62; H,7.63; N,10.60%.

(b) 3,4,5,6-Tetrahydro-N-[3-(morpholin-4-yl)propyl]
phthalimide (131 b)

General method (b) was employed.

The hydrochloride salt of the product was prepared and recrystallised from ethanol to give a white solid (20.8 g, 66%) mp: 211 - 214 °C. Neutralisation and evaporation of the dichloromethane extract gave a pale yellow oil (15.3 g, 55%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1763(w), 1705(s), 1675(shoulder). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 3.70 - 3.45(m, 6H); 2.40 - 2.00(m, 10H); 1.80 - 1.65(m, 6H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 171.2, 141.5(intense), 67.0(intense), 56.4, 53.7 (intense), 36.0, 25.4, 21.4-(intense), 20.0(intense). Found: C,64.90; H,8.01; 10.01; $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$ requires: C,64.73; H,7.97; N,10.06%.

Phthalimide

(a) N-[2-(Morpholin-4-yl)ethyl] phthalimide(132 b)

General method (a) was employed.

The product was recrystallised from ethanol to give a white solid (20.0 g, 77%). mp: 129 - 131 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 1765(w), 1710(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.85 - 7.65(m, 4H); 3.90 - 3.60(m, 6H, including a triplet, J=7 Hz, at 3.83); 2.70 - 2.45(m, 6H, including a triplet, J=7 Hz, at 2.63). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 168.3, 133.9, 132.2, 123.2, 67.0(intense), 56.1, 53.5 (intense), 35.0. Found: C, 64.79; H, 6.31; N, 10.78; C₁₄H₁₆N₂O₃ requires: C, 64.60; H, 6.20; N, 10.76%.

(b) N-[3-(Morpholin-4-yl)propyl] phthalimide
(131 c)

General method (b) was employed.

The hydrochloride salt of the product was prepared and recrystallised from ethanol to give a white solid (20.2 g, 65%) mp: 238 - 240 °C. Neutralisation and evaporation of the dichloromethane extract gave a pale yellow oil (17.0 g, 62%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1770(m), 1710(s). ¹H-nmr(60 MHz, CDCl₃) δ/ppm : 7.90 - 7.65(m, 4H); 3.78(t, J=7 Hz, 2H); 3.55 - 3.45(m, 4H); 2.50 - 2.30(m, 6H); 1.86(quintet, J=7 Hz, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 168.4, 133.9, 132.4, 123.1, 66.8(intense), 56.5, 53.6(intense), 36.6, 24.8. Found: C, 65.70; H, 6.77; N, 10.29; C₁₅H₁₈N₂O₃ requires

HYDANTOIN MANNICH BASES

General Method

Formaldehyde (7.5 g, 40% w/v in water, 0.090 mol) and secondary amine (0.10 mol) were added to a suspension of hydantoin or 5,5-disubstituted hydantoin (0.10 mol) in ethanol, and the mixture was heated on a water bath for 10 minutes. The solution was cooled overnight and then filtered to obtain the crude product.

(a) 3-(Morpholin-4-ylmethyl)hydantoin (125 a)

The product was recrystallised from ethanol to give a white solid (12.9 g, 72%) mp: 134 - 136 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3300(w), 1760(m), 1700(s). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 6.59(broad, 1H, disappears on addition of D_2O); 4.24(s, 2H); 4.05(s, 2H); 3.90 - 3.60(m, 4H); 2.80 - 2.55(m, 4H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 172.3, 159.2, 66.9(intense), 60.4, 50.8(intense), 46.4. Found: C, 48.31; H, 6.70; N, 21.10; $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_3$ requires C, 48.24; H, 6.58; N, 21.10%.

(b) 1,3-Bis(morpholin-4-ylmethyl)hydantoin (126)

Formaldehyde (15.0 g, 40% w/v in water, 0.180 mol) and morpholine (17.4 g, 0.20 mol) were added to a suspension of hydantoin (10.0 g, 0.10 mol) in ethanol, and heated on a water bath for 10 minutes. The solution was cooled overnight and then filtered to obtain the crude product. The product was recrystallised from

ethanol to give a white solid (14.6 g, 54%). mp: 142 - 144 °C (lit.⁸² 144 - 145.5 °C). ir(Nujol) $\bar{\nu}$ /cm⁻¹: 1770(w), 1718(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 4.47(s, 2H); 4.10(s, 2H); 4.05(s, 2H); 3.90 - 3.55(m, 8H); 2.80 - 2.40(m, 8H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 171.0, 157.8, 66.9(intense), 66.7 (intense), 65.1, 60.6, 50.9(intense), 49.9. Mass Spectrum m/e = 298(M⁺), 100(base, C₅H₁₀NO).

(c) 5,5-Dimethyl-3-(morpholin-4-ylmethyl)hydantoin
(125 b)

The product was recrystallised from ethanol to give a white solid (14.5 g, 71%). mp: 154 - 156 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3248(m), 1768(m), 1724(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 6.64(broad, 1H, disappears on addition of D₂O); 4.42(s, 2H); 3.85 - 3.55(m, 4H); 2.80 - 2.50 (m, 4H); 1.45(s, 6H). Found: C, 52.69; H, 7.57; N, 18.59; C₁₀H₁₇N₃O₃ requires: C, 52.85; H, 7.54; N, 18.49%.

(d) 5,5-Diphenyl-3-(1,2,5,6-tetrahydropyridin-1-ylmethyl)hydantoin (125 c)

The product was recrystallised from ethanol to give a white solid (23.6 g, 76%). mp: 123 - 125 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3210(w), 3100(w), 1770(m), 1720(s), 1600(w). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 7.35(s, 10H); 5.63(s, 2H); 4.59(s, 2H); 3.30 - 3.00(m, 2H); 2.77(t, J=6 Hz, 2H); 2.35 - 1.95(m, 2H). Found: C, 72.48; H, 6.15; N, 11.98; C₂₁H₂₁N₃O₂ requires: C, 72.60; H, 6.09; N, 12.10%.

(e) 5,5-Diphenyl-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)hydantoin (125 d)

The product was recrystallised from a chloroform/petroleum ether mixture to give a white solid (27.4 g, 77%).

mp: 181 - 183 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3330(m), 1773(m), 1710(s), 1600(w). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.40(s, 10H); 7.25 - 7.05(m, 4H); 4.75(s, 2H); 3.84(s, 2H); 2.90(s, 4H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 174.7, 157.6, 139.2, 134.5, 133.7, 129.7, 128.8, 128.7, 128.5, 127.6, 126.8, 126.6, 126.1, 125.8, 125.6, 70.4, 60.6, 52.5, 48.5, 29.3. Found: C, 75.69; H, 5.91; N, 10.47; $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2$ requires: C, 75.55; H, 5.83; N, 10.57%.

(f) 3-(Morpholin-4-ylmethyl)-5,5-diphenylhydantoin (125 e)

The product was recrystallised from propan-2-ol to give a white solid (24.6 g, 78%). mp: 159 - 161 °C, (lit.⁷⁵ 156 - 157 °C). ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3300(m), 1772(m), 1708(s), 1600(w). ^1H -nmr(60 MHz, CDCl_3) δ/ppm : 7.80 (broad, 1H, disappears on the addition of D_2O); 7.39(s, 10H); 4.49(s, 2H); 3.85 - 3.55(m, 4H); 2.80 - 2.45(m, 4H). Found: C, 68.27; H, 6.27; N, 11.82; $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$ requires: C, 68.36; H, 6.02; N, 11.96%.

(g) 3-(Dimethylaminomethyl)-5,5-diphenylhydantoin (125 f)

The product was recrystallised from ethanol to give a white solid (20.4 g, 73%). mp: 117 - 118 °C, (lit.⁷⁵

114 - 115 °C). ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3180(w), 3100(w),
1768(m), 1720(s), 1600(w). ¹H-nmr(60 MHz, CDCl₃)
δ/ppm: 7.81(broad, 1H, disappears on addition of D₂O);
7.39(s, 10H); 4.43(s, 2H); 2.27(s, 6H). ¹³C-nmr(90
MHz, CDCl₃) δ /ppm: 174.5, 157.7, 139.3, 128.8, 128.5,
126.8, 70.3, 61.5, 42.7(intense). Found: C, 70.01;
H, 6.23; N, 13.39; C₁₈H₁₉N₃O₂ requires: C, 69.88; H, 6.19;
N, 13.58%.

DIHYDROURACIL MANNICH BASES

General Method

Formaldehyde (15.0 g, 40% w/v in water, 0.180 mol) and secondary amine (0.20 mol) were mixed together. Dihydrouracil (0.10 mol) was added, and the mixture warmed until a solution formed. After cooling all volatiles were removed in vacuo, and a hydrochloride salt was prepared as described under the general procedure for the preparation of hydrochloride salts.

(a) 3-(Morpholin-4-ylmethyl)dihydrouracil (127 a)

The hydrochloride salt was recrystallised from ethanol to give a white solid (19.5 g, 78%). mp: 151 - 153 °C. The neutralised product was recrystallised from ethanol to give a white solid (14.5 g, 68%). mp: 152.5 - 154.4 °C. $\text{ir}(\text{Nujol}) \bar{\nu} / \text{cm}^{-1}$: 3203(w), 3090(w), 1730(m), 1680(s). $^1\text{H-nmr}$ (60 MHz, CDCl_3) δ/ppm : 8.55(broad, 1H, disappears on addition of D_2O); 4.15 (s, 2H); 3.75 - 3.65(m, 4H); 3.53(t, $J=7$ Hz, 2H); 2.80 - 2.35(m, 6H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 170.0, 153.4, 68.5, 66.8(intense), 50.9(intense), 41.6, 31.1. Found: C, 50.63; H, 7.15; N, 19.80; $\text{C}_9\text{H}_{15}\text{N}_3\text{O}_3$ requires: C, 50.69; H, 7.09; N, 19.71%.

(b) 3-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)dihydrouracil (127 b)

The product was prepared as described in the general

method, except that methanol had to be added to the reaction mixture to form a solution when warmed. The hydrochloride salt was recrystallised from ethanol to give a white solid (20.4 g, 69%). mp: 184 - 186 °C. The neutralised product was recrystallised from ethanol to give a white solid (16.6 g, 64%). mp: 124 - 126 °C. $\bar{\nu}$ (Nujol) /cm⁻¹: 3200(w), 3079(w), 1728(m), 1680(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 8.84(broad, 1H, disappears on addition of D₂O); 7.11(s, 4H); 4.30(s, 2H); 3.75(s, 2H); 3.53(t, J=7 Hz, 2H); 2.88(s, 4H); 2.61(t, J=7 Hz, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.2, 153.4, 134.1, 134.0, 128.7, 126.6, 126.3, 125.7, 67.9, 53.1, 48.3, 41.2, 31.1, 29.0. Found: C, 64.77; H, 6.44; N, 15.97; C₁₄H₁₇N₃O₂ requires: C, 64.85; H, 6.61; N, 16.20%.

(c) 3-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)dihydro-uracil (127 c)

The hydrochloride salt was recrystallised from ethanol to give a white solid (20.1 g, 82%). mp: 176 - 178 °C. The neutralised product was recrystallised from ethanol to give a white solid (14.4 g, 69%). mp: 107 - 109 °C. $\bar{\nu}$ (Nujol) /cm⁻¹: 3200(w), 3080(w), 1730(m), 1675(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm: 8.78(broad, 1H, disappears on addition of D₂O); 5.70(s, 2H); 4.22(s, 2H); 3.55(t, J=7 Hz, 2H); 3.25 - 2.95(m, 2H); 2.80 - 2.50(m, 4H); 2.35 - 2.00(m, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.6, 153.8, 125.4(intense), 68.2, 50.1, 47.7, 41.9, 31.5, 26.2. Found: C, 57.26; H, 7.51; N, 19.99; C₁₀H₁₅N₃O₂ requires: C, 57.40; H, 7.23; N, 20.08%.

(d) 3-(Piperidin-1-ylmethyl)dihydrouracil (127 d)

The hydrochloride salt was recrystallised from ethanol to give a white solid (18.1 g, 73%). mp: 175 - 177 °C. The neutralised product was recrystallised from ethanol to give a white solid (13.1 g, 62%). mp: 109 - 111 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3225(w), 1725(m), 1680(s). ¹H-nmr(60 MHz, CDCl₃) δ /ppm; 8.74(broad, 1H, disappears on addition of D₂O); 4.11(s, 2H); 3.55(t, J=7 Hz, 2H); 2.65(t, J=7 Hz, 2H); 2.50 - 2.45(m, 4H); 1.50 - 1.30(m, 6H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.4, 153.6, 69.0, 51.9(intense), 41.8, 31.4, 26.0(intense), 24.5. Found: C, 56.74; H, 7.97; N, 20.09; C₁₀H₁₇N₃O₂ requires: C, 56.85; H, 8.11; N, 19.89%.

C H A P T E R S E V E N

EXPERIMENTAL DATA FOR THE SUCCINIMIDE AND GLUT-
ARIMIDE PHOTOPRODUCTS

2-Hydroxy-6,8-diaza-11-oxatricyclo[6.4.0.0^{2,6}]dodecan-5-one (65 a)

N-(Morpholin-4-ylmethyl)succinimide (2.0 g) was irradiated for 8 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using 20% acetone/80% chloroform as the eluent gave starting material (0.65 g), then (65 a): first isomer (0.24 g, 18%) as a colourless semi-solid. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3385(sharp), 1680(s). ¹H-nmr(220 MHz, CDCl_3) δ/ppm : 4.38(d, J=6 Hz, 1H); 4.16(dd, J=11 and 3 Hz, 1H); 3.90 - 3.85(m, 1H); 3.79(d, J=6 Hz, 1H); 3.50 - 3.70(m, 3H, including 3.66 dd, J=11 and 3 Hz); 2.90 - 3.20(m, 2H); 2.58(dt, J=11 and 3/4 Hz, 1H); 2.45(ddd, J=17, 7/8 and 4 Hz, 1H); 2.33 (dd, J=9/10 and 3 Hz, 1H); 2.19(m, 2H). ¹³C-nmr(90 MHz, CDCl_3) δ/ppm : 175.9, 95.1, 67.7, 66.3, 65.7, 64.6, 50.0, 33.5, 30.7. Found: C, 54.44; H, 7.33; N, 13.99; $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 54.54; H, 7.12; N, 14.13%. The second isomer (0.80 g, 59%) was obtained as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3380(broad), 1695(s). ¹H-nmr(220 MHz, CDCl_3) δ/ppm : 4.90(broad, 1H); 4.52(d, J=9 Hz, 1H); 4.04(dd, J=11 and 5 Hz, 1H); 3.80 - 3.60(m, 2H); 3.05 - 2.95(m, 1H); 2.80(dd, J=7 and 4/5 Hz, 1H); 2.70 - 2.60(m, 2H); 2.50 - 2.35(m, 2H); 2.20 - 2.05(m, 2H). ¹³C-nmr(90 MHz, CDCl_3) δ/ppm : 180.0, 96.4, 67.4(intense), 65.0 (intense), 47.8, 31.9, 31.6. Mass Spectrum $m/e = 198(\text{M}^+)$, 180($\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$), 99(base, $\text{C}_5\text{H}_9\text{NO}$).

2-Hydroxy-6,8-diazatricyclo[6.4.0.0^{2,6}]dodecan-5-one

(65 b)

N-(Piperidin-1-ylmethyl)succinimide (2.0 g) was irradiated for 6 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using 20% acetone/80% chloroform as the eluent gave starting material (0.92 g), then (65 b): first isomer (0.14 g, 13%) as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3375(broad), 1700(s). ¹H-nmr(90 MHz, CDCl₃) δ/ppm : 4.45(broad, 1H); 4.28(d, J=6 Hz, 1H); 3.64(d, J=6 Hz, 1H); 3.30 - 0.90(m, 13H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 175.8, 95.8, 70.6, 64.8, 50.3, 30.1, 29.7, 24.7, 24.0, 23.0. Mass Spectrum m/e = 178(C₁₀H₁₄N₂O), 97(base, C₆H₁₁N). The second isomer (0.36 g, 33%) was obtained as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3380(broad), 1695(s). ¹H-nmr(90 MHz, CDCl₃) δ/ppm : 4.50(broad, 1H); 4.49(d, J=10 Hz, 1H); 3.36(d, J=10 Hz, 1H); 3.20 - 2.60 and 2.50 - 1.20(m, 13H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 180.6, 97.5, 71.7, 64.6, 49.0, 31.9, 31.3, 23.7. Found: C, 60.98; H, 8.10; N, 14.01; C₁₀H₁₆N₂O₂ requires: C, 61.20; H, 8.22; N, 14.27%.

3-Allyl-5-hydroxy-4-vinyl-1,3-diazabicyclo[3.3.0]-octan-8-one (65 c)

N-(Diallylaminomethyl)succinimide (2.0 g) was irradiated for 2½ hours using the 400-watt medium-pressure lamp. Separation by silica-gel column chromatography using an eluent ranging from chloroform to 5% methanol/95% chloroform gave starting material (0.48 g) then (65

c): first isomer (0.40 g, 26%) as a pale brown oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3350(broad) 3085(w), 1710(s), 1645(shoulder). $^1\text{H-nmr}$ (90 MHz, CDCl_3) δ/ppm : 6.00 - 5.10(m, 6H); 4.28(d, J=6 Hz, 1H); 3.82(d, J=6 Hz, 1H); 3.70 - 2.05(m, \sim 8H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 175.6, 133.2, 132.5, 121.7, 118.8, 96.0, 74.9, 63.4, 54.2, 32.9, 30.7. The second isomer was isolated (0.31 g, 20%) as a pale brown oil ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3380(broad), 3080(w), 1705(s), 1645(shoulder). $^1\text{H-nmr}$ (90 MHz, CDCl_3) δ/ppm : 6.15 - 4.90(m, 7H); 4.45(d, J=7/8 Hz, 1H); 3.45(d, J=7/8 Hz, 1H); 3.30 - 1.85(m, \sim 7H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 178.1, 134.4, 132.8, 120.9, 117.9, 97.8, 75.1, 63.2, 53.7, 31.9, 31.2. Also isolated was succinimide (0.13 g, 18%), identified by its infrared spectrum.

3-Ethyl-5-hydroxy-4-methyl-1,3-diazabicyclo [3.3.0] -
octan-8-one (65 d)

N-(Diethylaminomethyl)succinimide (2.0 g) was irradiated for 12 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using 20% acetone/80% chloroform as the eluent gave no starting material, then (65 d): first isomer (0.04 g, 2%) as a brown gum. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3385(broad), 1685(s). The only recognisable signals in the $^1\text{H-nmr}$ spectrum were δ/ppm : 4.35(d, J=6 Hz); 3.74(d, J= 6Hz). The second isomer (0.10 g, 5%) was obtained as a brown gum. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3380(broad), 1690(s). The only recognisable signals in the $^1\text{H-nmr}$ spectrum were δ/ppm :

4.43(d, J=6 Hz); 3.55(d, J=6 Hz). Also isolated was crude succinimide (1.10 g, 102%), identified by its infrared spectrum.

2-Hydroxy-6,8-diazatricyclo[6.4.0.0^{2,6}]dodec-11-en-5-one (65 e)

N-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)succinimide (2.0 g) was irradiated for 7 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.52 g), then a mixture (0.18 g, 12%) of two products which was further separated by repeated column chromatography to give 2-hydroxy-6,8-diazatricyclo[6.4.0.0^{2,6}]dodec-10-en-5-one as a brown gum. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3340 (broad), 3040(w), 1700(s), 1650(shoulder). ¹H-nmr(90 MHz, CDCl₃-acetone-d₆) δ/ppm : 5.80 - 5.75(m, 2H); 4.65(d, J=7 Hz, 1H); 3.41(d, J=7 Hz, 1H); 3.25 - 2.20(m, ~ 9H). ¹³C-nmr(90 MHz, CDCl₃-acetone-d₆) δ/ppm : 179.7, 124.5(intense), 97.4, 67.5, 65.1, 49.0, 32.2, 31.6, 25.1. Mass Spectrum m/e = 194(M⁺), 176(C₁₀H₁₂N₂O), 95(base, C₆H₉N). Then, first isomer of (65 e) was obtained as an off-white solid. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3150(broad), 3040(w), 1695(s), 1650(shoulder). ¹H-nmr(90 MHz, CDCl₃) δ/ppm : 6.10 - 5.65(m, 2H); 4.23 and 4.12(2d, J=6/7 Hz, 2H); 3.25 - 2.10(m, 10H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 175.8, 130.2, 120.7, 95.5, 67.2, 64.5, 46.0, 33.6, 30.6, 25.7. Mass Spectrum m/e

= 194(M⁺), 176(C₁₀H₁₂N₂O), 95(base, C₆H₉N). The second isomer of (65 e) was obtained as a colourless semi-solid (0.83 g, 56%). ir (CH₂Cl₂) $\bar{\nu}$ /cm⁻¹: 3350 (broad), 3045(w), 1685(s), 1650(shoulder). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 6.20 - 5.85(m, 2H); 4.49(d, J=10 Hz, 1H); 4.12(d, J=10 Hz, 1H); 3.90(broad, 1H); 3.65 - 3.60(m, 1H); 3.35 - 1.85(m, 8H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 178.0, 128.2, 122.2, 97.6, 67.3, 64.9, 43.8, 32.5, 32.3, 23.9. Mass Spectrum ^m/e = 194(M⁺), 176(C₁₀H₁₂N₂O), 95(base, C₆H₉N).

16-Hydroxy-10,12-diazatetracyclo [8.6.0.0.^{2,7}0^{12,16}]-hexadeca-2,4,6-trien-13-one (65 f)

N-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)succinimide (2.0 g) was irradiated for 7 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using 20% acetone/80% chloroform as the eluent gave starting material (0.59 g), then (65 f): first isomer(0.1 g, 7%) as a colourless oil. ir(thin film) $\bar{\nu}$ /cm⁻¹: 3380(broad), 1700(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 7.13(narrow m, 4H); 4.30(d, J=7 Hz, 1H); 4.09(d, J=7 Hz, 1H); 3.59(s, 1H); 3.40 - 2.30(m, 9H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm; 176.4, 135.7, 131.3, 127.7, 126.2, 125.9, 96.2, 70.0, 64.5, 47.0, 34.1, 32.9, 29.2. The second isomer (0.62 g, 44%) was obtained as a white solid, mp: 82 - 85 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3375(broad), 1695(s). ¹H-nmr(90 MHz, CDCl₃-acetone-d₆) δ /ppm: 7.30 - 7.10(m, 4H); 4.67(d, J=10/11 Hz, 1H); 4.40(very broad, 1H); 4.33(s,

1H); 4.20(d, J=10/11 Hz, 1H); 3.30 - 1.30(m, 8H).
 ^{13}C -nmr(90 MHz, CDCl_3 -acetone- d_6) δ /ppm: 178.8,
134.9, 132.7, 131.2, 129.3, 127.3, 126.7, 99.2,
70.7, 66.7, 45.4, 34.8, 32.2, 29.4. Found: C,68.71;
H,6.77; N,11.52; $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$ requires: C,68.84;
H,6.60; N,11.47%.

Attempted acid dehydration of (65 f)

Concentrated hydrochloric acid (100 mg) was added to the second isomer of (65 f, 100 mg) in chloroform (5 cm^3) and stirred at room temperature. T.L.C. of the mixture after various time intervals showed it to be a complex mixture.

The second isomer of (65 f, 200 mg) and sodium acetate (20 mg) in acetic anhydride (10 cm^3) were refluxed for 30 minutes. The solution went black and T.L.C. showed it to be a complex mixture.

The second isomer of (65 f, 100 mg) in 18% aqueous hydrochloric acid (20 cm^3) was refluxed for 1 hour. T.L.C. showed the reaction mixture to contain many products.

Attempted reduction of (65 f)

The second isomer of (65 f, 50 mg) in tetrahydrofuran (2 cm^3) at 0 $^{\circ}\text{C}$ was added dropwise to a solution of borane-tetrahydrofuran complex (0.4 cm^3 , 1 molar solution in tetrahydrofuran) in tetrahydrofuran

(2 cm³) at 0 °C, and stirred for several hours.

T.L.C. of the reaction mixture showed it to contain many products.

The above procedure was repeated using lithium aluminium hydride in tetrahydrofuran, and using diisobutylaluminium hydride in tetrahydrofuran in place of the borane-tetrahydrofuran complex, but both reactions gave complex mixtures.

1-Hydroxy-7,9-diaza-4-oxatricyclo[7.4.0.0.^{2,7}]tridecan-10-one (66 a)

N-(Morpholin-4-ylmethyl)glutarimide (2.0 g) was irradiated for 7 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 7% methanol/93% chloroform gave starting material (0.30 g), then (66 a) as impure samples which could not be further separated by repeated column chromatography. The first isomer of (66 a, 0.13 g, 8%) was a brown gum. $\underline{\text{ir}}(\text{CH}_2\text{Cl}_2) \bar{\nu}/\text{cm}^{-1}$: 3200 (broad), 1610(s). The only recognisable signals in the $^1\text{H-nmr}$ spectrum were δ/ppm : 4.54(d, J=6 Hz). The second isomer was isolated (0.07 g, 4%) as a brown gum. $\underline{\text{ir}}(\text{CH}_2\text{Cl}_2) \bar{\nu}/\text{cm}^{-1}$: 3325(broad), 1615(s). The only recognisable signals in the $^1\text{H-nmr}$ spectrum were δ/ppm : 4.70(d, J=8 Hz); 4.22(d, J=8 Hz). Also isolated was glutarimide (0.48 g, 53%) identified by its infrared spectrum.

17-Hydroxy-10,12-diazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-
heptadeca-2,4,6-trien-13-one (66.b)

N-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)glutarimide (2.0 g) was irradiated for 4 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 6% methanol/94% chloroform gave starting material (0.35 g), then (66.b) first isomer (0.28 g, 17%) as a white solid. mp: 138.5 - 140.5 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3170(broad), 1605(s). ¹H-nmr(90 MHz, CDCl₃) δ/ppm : 7.21(s, 4H); 4.56(d, J=7/8 Hz, 1H); 4.16(d, J=7/8 Hz, 1H); 3.57(s, 1H); 3.50 - 1.70(m, 11H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 169.6, 136.0, 131.2, 129.3, 127.4, 126.0, 125.6, 88.7, 70.8, 66.7, 46.4, 32.9, 30.7, 29.3, 16.7. Found: C, 69.67; H, 6.95; N, 10.71; C₁₅H₁₈N₂O₂ requires: C, 69.75; H, 7.02; N, 10.85%. The second isomer (0.32 g, 19%) was obtained as a white solid. mp: 150 - 152 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3340(broad), 1620(s). ¹H-nmr(90 MHz, CDCl₃) δ/ppm : 7.25 - 7.10(m, 4H); 5.4(very broad, 1H); 4.99(d, J=10/11 Hz, 1H); 4.50(s, 1H); 4.38(d, J=10/11 Hz, 1H); 3.00 - 1.25(m, 10H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 170.4, 133.8, 131.0, 128.6, 127.7, 127.1, 126.0, 89.5, 73.0, 67.1, 45.1, 33.5, 29.6, 28.6, 16.6. Found: C, 69.73; H, 7.11; N, 10.77; C₁₅H₁₈N₂O₂ requires: C, 69.75; H, 7.02; N, 10.85%.

Attempted acid dehydration of (66 b)

Concentrated hydrochloric acid (100 mg) was added to the second isomer of (66 b, 100 mg) in chloroform (5 cm³) and stirred at room temperature. T.L.C. of the mixture after various time intervals showed it to be a complex mixture.

The second isomer of (66 b, 100 mg) in 18% aqueous hydrochloric acid (20 cm³) was refluxed for 1 hour. T.L.C. showed the reaction mixture to contain many products.

2-Hydroxy-3-phenyl(or 4-phenyl)-6,8-diaza-11-oxatri-
cyclo[6.4.0.0^{2,6}]dodecan-5-one (80)

N-(Morpholin-4-ylmethyl)-2-phenylsuccinimide (2.0 g) was irradiated for 14 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.70 g) then (80) as a brown semi-solid (0.26 g, 20%). $\bar{\nu}(\text{CH}_2\text{Cl}_2)$ $\bar{\nu}/\text{cm}^{-1}$: 3345 (broad), 1700(s), 1605(w). $^1\text{H-nmr}$ (220 MHz, CDCl_3) δ/ppm : 7.45 - 7.25(m, 5H); 4.78(d, J=7 Hz, 1H); 4.65(very broad, 1H); 3.79(dd, J=9 and 3 Hz, 1H); 3.68(d, J=7 Hz, 1H); 3.55(dd, J=12 and 4 Hz, 1H); 3.40(t, J=9 Hz, 1H); 3.29(dd, J=11 and 3 Hz, 1H); 3.15(td, J=12 and 2/3 Hz, 1H); 2.85 - 2.75(m, 2H); 2.65 and 2.51(two d, J=3 Hz, 1H); 2.59(t, J=4 Hz, 1H); 2.19(t, J=11 Hz, 1H). $^{13}\text{C-nmr}$ (90 MHz,

CDCl_3) δ/ppm : 176.7, 138.3, 128.6, 127.9, 127.7, 99.0, 69.5, 63.9, 62.9, 62.1, 48.5, 48.1, 39.0.

Mass Spectrum $m/e = 274(\text{M}^+)$, $256(\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2)$, 99(base, $\text{C}_5\text{H}_9\text{NO}$). A mixture (0.18 g, 14%) of several other products could not be further separated by repeated column chromatography.

5-Hydroxy-3-methyl-6-phenyl-1,3-diazabicyclo[3.3.0]-octan-8-one (82) and 5-hydroxy-3-methyl-7-phenyl-1,3-diazabicyclo[3.3.0]octan-8-one (83)

N-(Dimethylaminomethyl)-2-phenylsuccinimide (2.0 g), was irradiated for 9 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.05 g), then (82 a) first isomer (0.32 g, 34%) as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3330(broad), 1700(s), 1605(w). $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ/ppm : 7.40 - 7.10(m, 5H); 4.65(broad, 1H); 4.15(d, $J=6$ Hz, 1H); 3.73(d, $J=6\text{Hz}$, 1H); 3.70(dd, $J=8\frac{1}{2}$ and $2\frac{1}{2}$ Hz, 1H); 3.44(dd, $J=17$ and $8\frac{1}{2}$ Hz, 1H); 2.62(dd, $J=17$ and $2\frac{1}{2}$ Hz, 1H); 2.55(d, $J=9\frac{1}{2}$ Hz, 1H); 2.44(s, 3H); 1.87(d, $J=9\frac{1}{2}$ Hz, 1H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 175.3, 139.7, 128.9, 127.5, 127.4, 99.0(s), 66.2(t), 62.4(t), 48.8(d), 39.8(q), 39.4(t). A mixture (0.48 g, 51%) of three other products was further separated by repeated column chromatography to give (82 b) second isomer as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3335(broad), 1700(s), 1605(w). $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ/ppm :

7.40 - 7.30(m, 5H); 4.16(d, $J=6\frac{1}{2}$ Hz, 1H); 3.89(d, $J=6\frac{1}{2}$ Hz, 1H), 3.66(dd, $J=12\frac{1}{2}$ and $7\frac{1}{2}$ Hz, 1H); 3.30(dd, $J=16$ and $12\frac{1}{2}$ Hz, 1H); 3.01(d, $J=9$ Hz, 1H); 2.83(d, $J=9$ Hz, 1H); 2.63(dd, $J=16$ and $7\frac{1}{2}$ Hz, 1H); 2.42(s, 3H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ /ppm: 175.1, 136.0, 128.9, 128.6, 128.4, 127.8, 126.3, 95.9(s), 66.3(t), 66.1(t), 51.1(d), 39.5(q), 37.8(t). (83 a) was obtained as a colourless oil. ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3335(broad) 1698(s), 1600(w). $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ /ppm: 7.50 - 7.25(m, 5H); 4.06(d, $J=6\frac{1}{2}$ Hz, 1H); 3.95(d, $J=6\frac{1}{2}$ Hz, 1H); 3.80(dd, $J=10\frac{1}{2}$ and $2\frac{1}{2}$ Hz, 1H); 3.01(d, $J=9\frac{1}{2}$ Hz, 1H); 2.71(dd, $J=14$ and $10\frac{1}{2}$ Hz, 1H); 2.53(d, $J=9\frac{1}{2}$ Hz, 1H); 2.39(dd, $J=14$ and $2\frac{1}{2}$ Hz, 1H); 2.40(s, 3H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ /ppm: 176.1, 139.2, 130.9, 128.8, 128.4, 127.6, 127.2, 94.8(s), 66.4(t), 66.3(t), 51.5(d), 39.7(q), 38.8(t). (83 b) was obtained impure as a gum, which could not be further purified by column chromatography. $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ /ppm: 174.8, 137.4, 130.9, 130.7, 128.7, 128.4, 127.3, 92.9, 66.7, 66.3, 49.8, 39.5, 37.8.

Irradiation of N-(morpholin-4-ylmethyl)pyrrolidin-2-one

(86, 0.3 g) was irradiated for 40 hours using the 125-watt medium-pressure lamp. T.L.C. showed the reaction mixture to be a complex mixture, with no major photoproducts.

Irradiation of N-(1,2,5,6-tetrahydropyridin-1-yl-methyl)pyrrolidin-2-one

(87, 2.0 g) was irradiated for 6 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 8% methanol/92% chloroform gave starting material (1.10 g) then N-(but-3-enylaminomethyl)pyrrolidin-2-one (88, 0.05 g, 5%) as a brown gum. ir(thin film) $\bar{\nu}$ /cm⁻¹: 3225(w), 3110(w), 1683(s), ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 6.15 - 5.50(m, 1H); 5.30 - 4.80(m, 2H); 4.24(s, 2H); 3.44(t, J=6 Hz, 2H); 2.95 - 1.80(m, 9H). ¹³C-nmr (90 MHz, CDCl₃) δ /ppm: 175.7(s), 136.2(d), 116.5(t), 57.3(t), 46.6(t), 45.6(t), 34.1(t), 31.3(t), 18.0(t). Mass Spectrum m/e = 127(C₆H₁₁N₂O), 113(C₅H₉N₂O), 98(base, C₅H₈NO), 84(C₄H₆NO), 70(C₄H₈N).

But-3-enylamine

A 1-litre three-necked flask was equipped with a reflux condenser, a mechanical stirrer and a dropping funnel. The flask was placed in an ice bath and charged with lithium aluminium hydride (4.94 g, 0.130 mol) and tetrahydrofuran (200 cm³). Sulphuric acid (6.37 g, 98%, 0.0650 mol) was slowly added through the dropping funnel over 10 minutes, while the solution was vigorously stirred. The stirring was continued for a further 1 hour. To the aluminium hydride solution, but-3-enenitrile (6.7 g, 0.10 mol) in tetrahydrofuran (20 cm³) was

added slowly. After stirring for a further 1 hour, the excess hydride was carefully destroyed by the addition of a mixture (50 cm³) of tetrahydrofuran and water (1:1) Stirring was continued as sodium hydroxide (15 g) in water (150 cm³) was added to coagulate the precipitated aluminium hydroxide. The clear tetrahydrofuran solution was decanted, and the remaining mass was extracted twice with ether (100 cm³). The amine solution was treated with hydrochloric acid (60 cm³, 2M). The aqueous layer was evaporated to dryness, washed with ether, and then dried in vacuo.

Attempted preparation of N-(butylaminomethyl)pyrrolidin-2-one by amine exchange

N-(Dimethylaminomethyl)pyrrolidin-2-one (1.42 g, 0.010 mol) and butylammonium chloride (1.1 g, 0.010 mol) were refluxed in ethanol. T.L.C. after 30 minutes showed the reaction mixture to contain many products.

Attempted preparation of N-(but-3-enylaminomethyl)-pyrrolidin-2-one

The above procedure was repeated using but-3-enylammonium chloride (1.1 g, 0.010 mol) in place of butylammonium chloride. T.L.C. after 30 minutes showed the reaction mixture to contain many products.

N-(1,2,5,6-Tetrahydropyridin-1-ylmethyl)pyrrolidin-2-one by amine exchange

N-(Dimethylaminomethyl)pyrrolidin-2-one (1.42 g, 0.010 mol) and 1,2,5,6-tetrahydropyridinium chloride (1.20 g, 0.010 mol) were refluxed in ethanol. T.L.C. after 30 minutes showed the appearance of a product with the same R_f value as the previously prepared N-(1,2,5,6-tetrahydropyridin-1-ylmethyl)pyrrolidin-2-one (87).

N-(Bromomethyl)pyrrolidin-2-one (91)

Pyrrolidin-2-one (4.25 g, 0.050 mol) and formaldehyde (3.75 g, 40% w/v in water, 0.0460 mol) in the presence of potassium hydroxide (0.05 g, 1% based on pyrrolidin-2-one) were stirred at room temperature for 24 hours. All volatiles were removed, to leave a white semi-solid. Hydrogen bromide solution (9.0 g, 45% in glacial acetic acid, 0.050 mol) was added to the crude N-(hydroxymethyl)-pyrrolidin-2-one and stirred at room temperature for 24 hours. All volatiles were removed, the resulting residue was washed several times with toluene, and then dried in vacuo to give a pale yellow viscous oil, (7.8 g, 95%). $\text{ir}(\text{thin film}) \bar{\nu}/\text{cm}^{-1}$: 1690(s). $^1\text{H-nmr}(60 \text{ MHz, CDCl}_3) \delta/\text{ppm}$: 5.31(s, 2H); 3.55(t, J=6/7 Hz, 2H); 2.65 -1.90(m, 4H).

N,N-Bis(2-oxopyrrolidin-1-ylmethyl)butylamine

(92)

N-(Bromomethyl)pyrrolidin-2-one (1.78 g, 0.010 mol) and butylamine (1.10 g, 0.015 mol) were refluxed for 3 hours in tetrahydrofuran (10 cm³). After cooling the solvent was removed, and the residue separated by silica-gel column chromatography using 5% methanol/95% chloroform as the eluent. One major band was collected and evaporated to give a yellow oil (0.50 g, 37%). ir(thin film) $\bar{\nu}$ /cm⁻¹: 1690(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 4.18(s, 4H); 3.65 - 3.30(m, 4H); 2.65 - 1.85(m, 10H); 1.60 - 1.10(m, 4H); 1.00 - 0.80(m, 3H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 175.7, 60.5(intense), 49.9, 47.1(intense), 31.3(intense), 29.9, 20.3, 18.1(intense), 13.9.

N,N-Bis(2-oxopyrrolidin-1-ylmethyl)butylamine

(92)

Pyrrolidin-2-one(1.70 g, 0.020 mol), formaldehyde (1.50 g, 40% w/v in water, 0.0180 mol) and butylammonium chloride (1.10 g, 0.010 mol) were refluxed in ethanol (10 cm³) for 1 hour. After cooling, all volatiles were removed. The residue was neutralised with a saturated sodium bicarbonate solution, extracted three times with dichloromethane (20 cm³), dried over anhydrous magnesium sulphate, filtered and the solvent removed. Separation of the mixture by silica-gel column chromatography using 5% methanol/

95% chloroform as the eluent gave (92) as a colourless oil (1.4 g, 58%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 1690(s). ^1H -nmr(90 MHz, CDCl_3) δ/ppm : 4.18(s, 4H); 3.65 - 3.30(m, 4H); 2.65 - 1.85(m, 10H); 1.60 - 1.10(m, 4H); 1.00 - 0.80(m, 3H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 175.7, 60.5(intense), 49.9, 47.1(intense), 31.3(intense), 29.9, 20.3, 18.1(intense), 13.9.

N,N-Bis(2-oxopyrrolidin-1-yl-methyl)but-3-enylamine
(93)

Pyrrolidin-2-one (1.7 g, 0.020 mol), formaldehyde (1.5 g, 40% w/v in water, 0.0180 mol) and but-3-enyl-ammonium chloride (1.1 g, 0.010 mol) were refluxed in ethanol (10 cm^3) for 1 hour. After cooling all volatiles were removed. The residue was neutralised with a saturated sodium bicarbonate solution, extracted three times with dichloromethane (20 cm^3), dried over anhydrous magnesium sulphate, filtered and the solvent removed. Separation of the mixture by silica-gel column chromatography using 5% methanol/95% chloroform as the eluent gave (93) as a colourless oil (1.1 g, 46%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3070(w), 1690(s), 1650 (shoulder). ^1H -nmr (90 MHz, CDCl_3) δ/ppm : 6.15 - 5.50(m, 1H); 5.25 - 4.85(m, 2H); 4.20(s, 4H); 3.47(t, $J=6/7$ Hz, 4H); 2.90 - 1.70(m, 12H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 175.8, 136.6, 115.9, 60.4(intense), 49.7, 47.0 (intense), 32.2, 31.3(intense), 18.0(intense).

Irradiation of N-methyl-2-(morpholin-4-ylmethyl)-
2-phenylsuccinimide

(95 b, 0.10 g) was irradiated for 20 hours using the 125-watt medium-pressure lamp. T.L.C. showed the reaction mixture to contain many products, with no major photoproducts.

Irradiation of N-methyl-2-phenyl-2-(1,2,5,6-tetrahydropyridin-1-ylmethyl)succinimide

(95 c, 0.10 g) was irradiated for 20 hours using the 125-watt medium-pressure lamp. T.L.C. showed the reaction mixture to contain many products, with no major photoproducts.

2-Hydroxy-3-methyl-6-phenyl-3,8-diazatricyclo-
[6.4.0.0^{2,6}] dodecan-4-one (96 a)

N-Methyl-2-phenyl-2-(piperidin-1-ylmethyl)succinimide (0.50 g) was irradiated for 50 hours using the 125-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using chloroform as the eluent gave no starting material then (96 a) as a brown gum (0.025 g, 5%). $\text{ir}(\text{CH}_2\text{Cl}_2)$ $\bar{\nu}/\text{cm}^{-1}$: 3320(broad), 1670(s). $^1\text{H-nmr}$ (220 MHz, CDCl_3) δ/ppm : 7.55 - 7.20(m, 5H); 3.40 - 2.70(m, 9H, including strong singlet at 2.89, d, $J=15$ Hz at 2.78, d, $J=15$ Hz at 3.01, d, $J=9$ Hz at 3.03, d, $J=9$ Hz, at 3.09); 2.20 - 2.00(m, 3H); 2.00 - 1.80(m, 2H);

1.80 - 1.40(m, 3H). Mass Spectrum $m/e = 189(C_{11}H_{11}NO_2)$,
97(base, $C_6H_{11}NO$).

6-(Morpholin-4-yl)perhydroazepine-2,5 -dione (102)

N-[2-(Morpholin-4-yl)ethyl]succinimide (2.0 g) was irradiated for 3½ hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 6% methanol/94% chloroform gave starting material (1.01 g), then (102) as a white solid (0.45 g, 46%). mp: 176 - 178 °C. ir(Nujol) $\bar{\nu}/cm^{-1}$: 3320(w), 3200(w), 3100(w), 1710(m-s), 1680(s). 1H -nmr(220 MHz, $CDCl_3$) δ/ppm : 7.60(broad, 1H); 3.75(t, J=5 Hz, 4H); 3.59(td, J=16 and 6 Hz, 1H); 3.36(dd, J=16 and 5 Hz, 1H); 3.10 - 2.85(m, 2H); 3.36(dd, J= 16 and 5 Hz, 1H); 3.10 - 2.85(m, 2H); 2.75 - 2.25(m, 7H). ^{13}C -nmr(90 MHz, $CDCl_3$) δ/ppm : 220.5, 176.3, 74.9, 66.7(intense), 50.9 (intense), 40.7, 36.3, 31.6. Found: C,56.74; H,7.49; N,13.31; $C_{10}H_{16}N_2O_3$ requires: C,56.59; H,7.60; N,13.20%.

6-Dimethylaminoperhydroazepine-2,5-dione (103)

N-[2-(Dimethylamino)ethyl]succinimide (2.0 g) was irradiated for 5 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform gave

starting material (0.80 g), then (103) as a brown gum (0.20 g, 17%). $\text{ir}(\text{CH}_2\text{Cl}_2)$ $\bar{\nu}/\text{cm}^{-1}$: 3220(w), 3085(w), 1710(s), 1660(s). $^1\text{H-nmr}(220 \text{ MHz}, \text{CDCl}_3)$ δ/ppm : 7.56(broad, 1H); 3.53(td, $J=15\frac{1}{2}$ and 6 Hz, 1H); 3.36(dd, $J=15\frac{1}{2}$ and 5 Hz, 1H); 3.10 - 2.30(m, 11H, including strong singlet at 2.29). $^{13}\text{C-nmr}(90 \text{ MHz}, \text{CDCl}_3)$ δ/ppm : 210.5, 176.6, 75.7, 42.9(intense), 41.6, 36.3, 31.7. Mass Spectrum $m/e = 170(\text{M}^+)$, 126($\text{C}_6\text{H}_8\text{NO}_2$), 71(base, $\text{C}_4\text{H}_9\text{N}$).

7-(Morpholin-4-yl)perhydroazocine-2,6-dione (104)

N- [2-(Morpholin-4-yl)ethyl] glutarimide (2.0 g) was irradiated for 7 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.35 g), then (104) as a pale brown gum (0.50 g, 77%). $\text{ir}(\text{CH}_2\text{Cl}_2)$ $\bar{\nu}/\text{cm}^{-1}$: 3120(w), 3090(w), 1710(m), 1665(s). $^1\text{H-nmr}(90 \text{ MHz}, \text{CDCl}_3)$ δ/ppm : 6.77(broad, 1H); 3.80 - 3.45(m, 5H); 3.40 - 2.85(m, 2H); 2.75 - 1.70(m, 10H). $^{13}\text{C-nmr}(90 \text{ MHz}, \text{pyridine-d}_5)$ δ/ppm : 213.0, 175.3, 79.3, 66.9 (intense), 52.0(intense), 41.2, 36.4, 32.9, 23.6. Mass Spectrum $m/e = 198(\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2)$, 170($\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$), 141 ($\text{C}_7\text{H}_{11}\text{NO}_2$), 127($\text{C}_6\text{H}_9\text{NO}_2$), 113(base, $\text{C}_5\text{H}_7\text{NO}_2$ or $\text{C}_6\text{H}_{11}\text{NO}$).

5-(Morpholin-4-yl)-3-azabicyclo[5.4.0]undec-9-ene-
2,6-dione (105)

N-[2-(Morpholin-4-yl)ethyl]-1,2,3,6-tetrahydrophthalimide (2.0 g) was irradiated for 6 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.92 g), then (105) as a pale brown gum (0.80 g, 74%). ir(CDCl₃) $\bar{\nu}/\text{cm}^{-1}$: 3295(w), 3220(w), 3030(w), 1710(m-s), 1664(s), 1645(shoulder). ¹H-nmr(220 MHz, CDCl₃) δ/ppm : 6.91(broad, 1H); 5.77(s, 2H); 3.76(t, J=4½ Hz, 4H); 3.65 - 3.35(m, 3H); 3.20 - 3.05(m, 2H); 2.75 - 2.65(m, 2H); 2.45 - 2.20(m, 6H). ¹³C-nmr(90 MHz, CDCl₃) δ/ppm : 210.0, 175.7, 125.2(d), 124.8(d), 74.0(d), 66.8(intense, t), 50.8(intense, t), 44.4(d), 41.4(d), 40.4(t), 25.5(t), 25.0(t). Mass Spectrum m/e = 264(M⁺), 236(base, C₁₃H₂₀N₂O₂), 178(C₁₀H₁₂NO₂).

Attempted dehydrogenation of (105)

(105, 0.264 g, 0.0010 mol) and 2,3-dichloro- 5,6-dicyano-1,4-benzoquinone (0.454 g, 0.0020 mol) were refluxed in dry benzene (5 cm³) for several hours. T.L.C. of the reaction mixture showed it to contain many products.

7-Hydroxy-5-methyl-1,5-diazabicyclo[5.3.0]decan-10-one
(112)

N-[3-(Dimethylamino)propyl]succinimide (2.0 g) was irradiated for 8 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform gave starting material (0.78 g), then (112) as a pale brown oil (0.38 g, 31%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3340(broad), 1675(s). $^1\text{H-nmr}$ (220 MHz, CDCl_3) δ/ppm : 3.50(t, $J=5\frac{1}{2}$ Hz, 2H); 3.00 - 2.90(m, 1H); 2.80 - 2.65(m, 3H); 2.60 - 2.45(m, 4H, including s, 2.51); 2.40 - 2.30(m, 2H); 2.15 - 1.70(m, 4H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 174.4, 89.3(s), 65.0(t), 58.7(t), 47.6(q), 39.0(t), 31.5(t), 29.5(t), 27.1(t). Mass Spectrum m/e = 184(M^+), 166 ($\text{C}_9\text{H}_{14}\text{N}_2\text{O}$), 58(base, $\text{C}_3\text{H}_8\text{N}$).

2-Hydroxy-6,9-diaza-12-oxatricyclo[7.4.0.0.^{2,6}]-tridecan-5-one (113)

N-[3-(Morpholin-4-yl)propyl]succinimide (2.0 g) was irradiated for 8 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.45 g), then (113) as a brown semi-solid (0.07 g, 12%). ir(CH_2Cl_2) $\bar{\nu}/\text{cm}^{-1}$: 3335 (broad), 1685(s). $^1\text{H-nmr}$ (90 MHz, pyridine- d_5) δ/ppm : 4.45

- 3.40(m, ~ 6H); 3.40 - 1.80(m, ~ 12H). ^{13}C -nmr(90 MHz, pyridine- d_5) δ /ppm: 174.4, 92.4, 66.7, 66.3 (intense), 65.5, 57.2, 51.8, 36.0, 30.3, 29.2, 25.8. Also isolated was (114) as a brown gum (0.045 g, 8%). $\text{ir}(\text{CH}_2\text{Cl}_2)$ $\bar{\nu}/\text{cm}^{-1}$: 3295(w), 3250(w), 1645(s). ^{13}C -nmr(90 MHz, CDCl_3) δ /ppm: 178.9, 65.8(intense), 59.2, 53.9, 52.7(intense), 40.8, 31.1, 28.5(intense).

Irradiation of N-[4-(dimethylamino)butyl]succinimide

(101 b, 2.0 g) was irradiated for 3½ hours using the 400-watt medium-pressure lamp. The mixture could not be separated by silica-gel column chromatography.

Irradiation of N-[5-(dimethylamino)pentyl]succinimide

(101 c, 2.0 g) was irradiated for 4 hours using the 400-watt medium-pressure lamp. The mixture could not be separated by silica-gel column chromatography.

6-[2-(Morpholin-4-yl)ethyl]perhydroazepine-2,5-dione (117) and 5-hydroxy-4-morpholin-4-ylmethyl-1-azabicyclo[3.3.0]octan-8-one (118)

N-[4-(Morpholin-4-yl)butyl]succinimide (2.0 g) was irradiated for 6 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform

gave starting material (1.30 g), then (117) as a brown gum (0.18 g, 26%). ir(CDCl₃) $\bar{\nu}$ /cm⁻¹: 3210(w), 3080(w), 1700(s), 1670(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 7.35(broad, 1H); 3.75 - 3.30(m, 4H); 3.45 - 3.20(m, 2H); 2.70 - 2.25(m, ~11H); 2.05 - 1.40(m, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 209.6, 176.3, 66.8(intense, t), 56.0(t), 53.6(intense, t), 52.2(d), 43.0(t), 38.0(t), 30.9(t), 25.4(t). The second product (118) was obtained as a brown gum (0.09 g, 13%). ir(CDCl₃) $\bar{\nu}$ /cm⁻¹: 3345(broad), 1695(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 3.80 - 3.60(m, ~4H); 3.40 - 2.80(m, ~4H); 2.75 - 2.35(m, ~8H); 2.25 - 1.95(m, ~4H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 174.5, 97.7(s), 66.9(intense, t), 58.0(t), 54.3(intense, t), 44.6(d), 39.8(t), 33.5(t), 30.5(t).

C H A P T E R E I G H T

EXPERIMENTAL DATA FOR THE HYDANTOIN, 5,5-DISUBSTITUTED
HYDANTOINS AND DIHYDROURACIL PHOTOPRODUCTS

2-Hydroxy-11-oxa-4,6,8-triazatricyclo[6.4.0.0^{2,6}]-
dodecan-5-one (128)

3-(Morpholin-4-ylmethyl)hydantoin (2.0 g) was irradiated for 3 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform gave starting material (0.65 g) then a mixture (0.84 g, 62%) of stereoisomers of (128). One of the isomers was isolated as white crystals (mp: 137.5 - 139 °C) by partial crystallisation from chloroform. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3345(broad), 3200(w), 3100(w), 1710(s). ¹H-nmr(90 MHz, pyridine-d₅) δ/ppm : 8.05(broad, 1H); 4.60 - 3.40(m, 9H, including two doublets at 4.55 and 4.04, $J=4\frac{1}{2}$ Hz); 2.90 - 2.30(m, 3H). ¹³C-nmr(90 MHz, pyridine-d₅) δ/ppm : 164.2, 93.9, 69.1, 66.7, 66.6, 65.9, 50.3, 50.1. Mass Spectrum $m/e = 199(M^+)$, 181(C₈H₁₁N₃O₂), 99(base, C₅H₉NO). Found: C, 48.16; H, 6.52; N, 21.27; C₈H₁₃N₃O₃ requires: C, 48.24; H, 6.58; N, 21.10%. The signals for the ¹³C-nmr spectrum of the second isomer were identified from the spectrum of the mixture: 166.4, 95.0, 70.2, 69.1, 66.4, 65.6, (50.3), 49.1. Also isolated was hydantoin (0.3 g, 44%), identified by its infrared spectrum.

2-Hydroxy-4-(morpholin-4-ylmethyl)-11-oxa-4,6,8-triazatri-
cyclo[6.4.0.0^{2,6}]dodecan-5-one (129)

1,3-Bis(morpholin-4-ylmethyl)hydantoin (2.0 g) was irradiated for 2½ hours using the 400-watt medium-

pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 20% methanol/80% chloroform gave starting material (0.70 g), then a mixture (1.0 g, 77%) of stereoisomers of (129). The isomers were separated by repeated column chromatography. The first isomer was obtained as white crystals (mp: 123- 125 °C).

ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3285(broad), 1685(s). ¹H-nmr(400 MHz, CDCl₃) δ /ppm: 4.35(d, J=5 Hz, 1H); 3.99(dd, J=11½ and 3½ Hz, 1H); 3.93(d, J=12½ Hz, 1H); 3.80(d, J=12½ Hz, 1H); 3.65 - 3.45(m, 10H, including two doublets 3.60 and 3.47, J=10 Hz); 2.95(td, J=11 and 2½ Hz, 1H); 2.50 - 2.45(m, 6H); 2.19(dd, J=9 and 3 Hz, 1H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 161.2, 90.5, 68.7, 66.7(intense), 66.1(intense), 65.8, 65.6, 52.7, 50.8(intense), 49.9. Mass Spectrum ^m/e = 298(M⁺), 280(C₁₃H₂₀N₄O₃), 100(base, C₅H₁₀NO), 99(C₅H₉NO). Found: C, 52.22; H, 7.49; N, 18.80; C₁₃H₂₂N₄O₄ requires: C, 52.34; H, 7.43; N, 18.78%.

The second isomer was obtained as a colourless oil.

ir(thin film) $\bar{\nu}$ /cm⁻¹: 3360(broad), 1700(s). ¹H-nmr(90 MHz, pyridine-d₅) δ /ppm: 4.84(d, J=8 Hz, 1H); 4.35 - 3.40(m, 13H); 3.05 - 2.95(m, 1H); 2.80 - 2.30(m, 6H). ¹³C-nmr(90 MHz, pyridine-d₅) δ /ppm: 164.4, 92.2, 70.0, 69.5, 66.9(intense), 66.5, 66.1, 65.7, 54.4, 51.3(intense), 49.1. Mass Spectrum ^m/e = 298(M⁺), 280(C₁₃H₂₀N₄O₃), 100(base, C₅H₁₀NO), 99(C₅H₉NO).

Also isolated was hydantoin (0.16 g, 37%) identified by its infrared spectrum.

2-Hydroxy-3,3-dimethyl-4,6,8-triaza-11-oxatricyclo-
[6.4.0.0^{2,6}]dodecan-5-one (130 a)

5,5-Dimethyl-3-(morpholin-4-ylmethyl)hydantoin (2.0 g) was irradiated for 3½ hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.06 g), then (130 a) as a white solid (0.56 g, 60%). mp: 168 - 170 °C. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3335(broad), 3210(w), 1710(s). ¹H-nmr(220MHz, pyridine-d₅) δ/ppm : 7.2(broad, 1H); 5.0(broad, 1H); 4.50(d, J=5 Hz, 1H); 4.33(dd, J=11 and 3 Hz, 1H); 4.23(d, J=5 Hz, 1H); 4.01(t, J=10½ Hz, 1H); 3.84(dd, J=11 and 3 Hz, 1H); 3.57(td, J=11 and 3Hz, 1H); 2.92(broad d, J=11 Hz 1H); 2.74(dd, J=10 and 3 Hz, 1H); 2.54(td, J=11 and 3 Hz, 1H); 1.64(s, 3H); 1.42(s, 3H). ¹³C-nmr(90 MHz, pyridine-d₅) δ/ppm : 162.6, 97.2, 68.3, 67.8, 65.7, 63.7, 57.9, 50.7, 26.6, 25.1. Mass Spectrum $m/e = 227(\text{M}^+)$, 209(C₁₀H₁₅N₃O₂), 99 (base, C₅H₉NO). Found: C, 52.78; H, 7.63; N, 18.60; C₁₀H₁₇N₃O₃ requires: C, 52.85; H, 7.54; N, 18.49%.

16-Hydroxy-15,15-diphenyl-10,12,14-triazatetracyclo-
[8.6.0.0^{2,7}. 0^{12,16}]hexadeca-2,4,6-trien-13-one (130 b)

5,5-Diphenyl-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)hydantoin (2.0 g) was irradiated for 2 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography

using an eluent ranging from chloroform to 6% methanol/
 94% chloroform gave starting material (0.99 g),
 then (130 b) as a white solid (0.73 g, 72 %). mp:
 176 - 178 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3400(sharp), 3100(w),
 3040(w), 1722(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 7.40
 - 6.50(m, 13H); 6.08(s, 1H, reduced with D₂O); 5.38(d,
 J=7 Hz, becomes a singlet with selective decoupling
 at 6.72 ppm); 4.85(d, J=8 Hz, 1H); 4.46(s, 1H);
 4.05(d, J=8 Hz, 1H); 3.40 - 2.30(m, 5H, reduces
 to 4H with D₂O). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 161.1,
 141.9, 139.3, 130.2, 129.4, 129.1, 128.7, 128.5,
 128.2, 127.8, 127.3, 125.5, 98.8, 71.9, 65.2, 65.0,
 47.1, 26.7. Mass Spectrum ^m/e = 397(M⁺), 252(C₁₅H₁₂N₂O₂),
 145(base, C₁₀H₁₁N). Found: C, 75.48; H, 6.00; N,
 10.31; C₂₅H₂₃N₃O₂ requires: C, 75.55; H, 5.83; N,
 10.57%.

2-Hydroxy-3,3-diphenyl-4,6,8-triazatricyclo[6.4.0.0^{2,6}]-
 dodec-11-en-5-one (130 c)

5,5-Diphenyl-3-(1,2,5,6-tetrahydropyridin-1-ylmethyl)-
 hydantoin (2.0 g) was irradiated for 2 hours using
 the 400-watt medium-pressure lamp. Separation of
 the mixture by silica-gel column chromatography,
 using an eluent ranging from chloroform to 8% methanol/
 92% chloroform gave starting material (0.58 g),
 then (130 c) as a white solid (0.60 g, 42%). mp:
 134 - 136 °C. ir(Nujol) $\bar{\nu}$ /cm⁻¹: 3225(broad); 3060(w),
 1700(s), 1600(w). ¹H-nmr(90 MHz, pyridine-d₅) δ /ppm:
 9.70(broad, 1H); 8.20 - 7.10(m, 10H); 5.70 - 5.20(m,
 2H); 4.95(d, J=6 Hz, 1H); 4.27(d, J=6 Hz, 1H); 4.20

(broad, 1H); 3.0 - 1.20(m, 5H). ^{13}C -nmr(90 MHz, pyridine- d_5) δ /ppm: 162.6, 144.9, 142.5, 129.5, 128.9, 128.5, 127.9, 127.7, 127.3, 125.8, 99.7, 69.6, 66.5, 62.4, 42.4, 18.5. Mass Spectrum m/e = 95(base, $\text{C}_6\text{H}_9\text{N}$).

2-Hydroxy-3,3-diphenyl-11-oxa-4,6,8-triazatricyclo-
[6.4.0.0^{2,6}]dodecan-5-one (130 d)

3-(Morpholin-4-ylmethyl)-5,5-diphenylhydantoin (2.0 g), was irradiated for 6 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.92 g), then (130 d) as a colourless oil (0.39 g, 36%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3230 (broad), 3090(w), 3060(w), 1710(s), 1598(w). ^1H -nmr(90 MHz, pyridine- d_5) δ /ppm: 9.60(broad, 1H); 8.10 - 7.20(m, 10H); 4.56(d, $J=5$ Hz, 1H); 4.39(d, $J=5$ Hz, 1H); 3.75 - 3.20(m, 4H); 3.00 - 2.40(m, 4H). ^{13}C -nmr(90 MHz, pyridine- d_5) δ /ppm: 163.7, 145.7, 140.9, 130.1, 129.1, 128.6, 128.3, 128.2, 127.9, 127.6, 127.2, 99.4, 69.7, 68.4, 67.6, 65.4, 64.5, 50.4. Mass Spectrum m/e = 351(M^+), 333($\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$), 252($\text{C}_{15}\text{N}_{12}\text{N}_2\text{O}_2$), 99(base, $\text{C}_5\text{H}_9\text{NO}$).

5-Hydroxy-7-methyl-4,4-diphenyl-1,3,7-triazabicyclo-
[3.3.0]octan-2-one (130 e)

3-(Dimethylaminomethyl)-5,5-diphenylhydantoin (2.0 g) was irradiated for 6 hours using the 400-watt

medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.54 g), then (130 e) as a sticky solid (0.24 g, 52%) from which white crystals (mp: 103 - 105 °C) were isolated by repeated column chromatography. ir(Nujol) $\bar{\nu}/\text{cm}^{-1}$: 3240(broad), 1710(s), 1600(w). $^1\text{H-nmr}$ (90 MHz, CDCl_3) δ/ppm : 7.45 - 7.15(m, 11H); 4.33(d, $J=7/8$ Hz, 1H); 3.89(d, $J=7/8$ Hz, 1H); 2.72(d, $J=11$ Hz, 1H); 2.62(s, 1H); 2.47(d, $J=11$ Hz, 1H); 2.29(s, 3H). $^1\text{H-nmr}$ (90 MHz, pyridine- d_5) δ/ppm : 9.95(broad, 1H); 8.15 - 7.05(m, 10H); 4.91(d, $J=7/8$ Hz, 2H); 4.08(d, $J=7/8$ Hz, 1H); 3.07(s, 2H); 2.41(s, 3H). $^1\text{H-nmr}$ (90 MHz, methanol- d_4) δ/ppm : 7.50 - 7.00(m, 10H); 4.50(d, $J=8$ Hz, 1H); 3.77(d, $J=8$ Hz, 1H); 2.74(d, $J=11$ Hz, 1H); 2.56(d, $J=11$ Hz, 1H); 2.39(s, 3H). $^{13}\text{C-nmr}$ (90 MHz, CDCl_3) δ/ppm : 162.5, 140.9, 139.1, 128.8, 128.3, 127.9, 126.3, 99.4, 69.5, 69.3, 63.3, 41.4. $^{13}\text{C-nmr}$ (90 MHz, pyridine- d_5) δ/ppm : 163.4, 147.9, 142.8, 129.4, 128.6, 128.1, 127.6, 127.1, 100.1, 70.4, 70.1, 65.2, 41.6. Mass Spectrum m/e = 309(M^+), 57(base, $\text{C}_3\text{H}_7\text{N}$).

IRRADIATION OF DIHYDROURACIL MANNICH BASES

Irradiation of 3-(morpholin-4-ylmethyl)dihydrouracil

(127 a, 200 mg) was irradiated for 15 hours using the 125-watt medium-pressure lamp. T.L.C. showed the reaction mixture to contain nearly all starting material and many minor photoproducts.

Irradiation of 3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)dihydrouracil

(127 b, 200 mg) was irradiated for 14 hours using the 125-watt medium-pressure lamp. T.L.C. showed the reaction mixture to contain nearly all starting material and many minor photoproducts.

CHAPTER NINE

EXPERIMENTAL DATA FOR THE MALEIMIDE AND PHTHALIMIDE
PHOTOPRODUCTS

2-Hydroxy-6,9-diaza-12-oxatricyclo[7.4.0.0^{2,6}]tridec-3-en-5-one (134 a)

N-[2-(Morpholin-4-yl)ethyl]maleimide (0.5 g) was irradiated for 4 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 8% methanol/92% chloroform gave starting material (0.12 g), then (134 a) first isomer (0.08 g, 21%) as a pale yellow oil. ir(thin film) $\bar{\nu}$ /cm⁻¹: 3360(broad), 3100(w), 1690(s), 1590(w). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 6.90(d, J=6 Hz, 1H); 6.22(d, J=6 Hz, 1H); 3.90 - 3.65(m, 7H); 2.70 - 2.45(m, 5H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 166.4, 145.2, 129.7, 86.5, 67.0, 66.9, 66.5, 54.5, 53.9, 35.4. Mass Spectrum m/e = 210(M⁺), 100(base, C₅H₁₀NO). The second isomer (0.05 g, 13%) was obtained as a pale yellow waxy solid. ir(CH₂Cl₂) $\bar{\nu}$ /cm⁻¹: 3340 (broad), 3090(w), 1700(s), 1590(w). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 6.85(d, J=6 Hz, 1H); 6.14(d, J=6 Hz, 1H); 4.10 - 3.50(m, 4H); 3.40 - 2.95(m, 6H); 2.85 - 2.45(m, 2H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 167.4, 145.9, 128.6, 87.1, 66.9, 62.6, 60.8, 53.3, 44.3, 34.6. Mass Spectrum m/e = 210(M⁺), 192 (C₁₀H₁₂N₂O₂), 98(base, C₅H₈NO). Also isolated was a third product (135, 0.08 g, 11%) as a light brown oil. ir(thin film) $\bar{\nu}$ /cm⁻¹: 1775(w), 1705(s). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 3.80 - 3.55 and 2.75 - 2.40(multiplets in a ratio of 4:5 respectively). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 175.8, 174.9, 67.0(intense, t), 62.5(d), 55.1(t), 53.4(intense, t), 49.4(t),

35.4(t), 31.1(t), 28.1(t). Mass Spectrum $m/e =$
212(M^+), 100(base, $C_5H_{10}NO$).

1-Hydroxy-7,10-diaza-4-oxatetracyclo[8.7.0.0^{2,7}.
0^{12,17}]heptadec-12(17)-en-11-one (134 b)

3,4,5,6-Tetrahydro-N-[2-(morpholin-4-yl)ethyl]
phthalimide (2.0 g) was irradiated for 8 hours
using the 400-watt medium-pressure lamp. Separation
of the mixture by silica-gel column chromatography
using an eluent ranging from chloroform to 10%
methanol/90% chloroform gave starting material
(0.93 g), then (134 b) first isomer (0.25 g, 23%)
as a light brown gum. ir(CH_2Cl_2) $\bar{\nu}/cm^{-1}$: 3320(broad),
3050(w), 1690(s), 1660(shoulder). ¹H-nmr(90 MHz,
 $CDCl_3$) δ/ppm : 4.20 - 3.00(m, 7H); 2.90 - 2.60(m,
2H); 2.50 - 1.25(m, 11H). ¹³C-nmr(90 MHz, $CDCl_3$)
 δ/ppm : 167.6, 153.3, 133.9, 85.9, 66.7(intense),
66.5, 54.3(intense), 35.5, 23.2, 22.3, 21.5, 20.2.
Mass Spectrum $m/e =$ 264(M^+), 246($C_{14}H_{18}N_2O_2$),
100(base, $C_5H_{10}NO$). The second isomer (0.16 g,
15%) was obtained as a light brown gum. ir(CH_2Cl_2)
 $\bar{\nu}/cm^{-1}$: 3320(broad), 3055(w), 1695(s), 1665(shoulder).
¹H-nmr(90 MHz, $CDCl_3$) δ/ppm : 4.55 - 3.60(m, 3H);
3.50 - 1.95(m, 13H); 1.85 - 1.40(m, 4H). ¹³C-nmr(90
MHz, $CDCl_3$) δ/ppm : 167.4, 151.8, 134.1, 85.5, 61.2,
60.0, 58.8, 53.3, 43.3, 34.4, 21.7(intense), 21.2,
20.0. Mass Spectrum $m/e =$ 264(M^+), 246($C_{14}H_{18}N_2O_2$),
100(base, $C_5H_{10}NO$).

Acid dehydration of (134 b)

The second isomer of (134 b) (100 mg) was refluxed in 18% aqueous hydrochloric acid (20 cm³) for 1 hour. After cooling the reaction mixture was neutralised with sodium bicarbonate and extracted three times with dichloromethane (30 cm³). The organic layer was dried over anhydrous magnesium sulphate and filtered. Removal of the solvent gave a dark brown residue, which was separated by silica-gel column chromatography using 5% methanol/95% chloroform as the eluent. One major band was collected and evaporated to give a bright yellow oil of (138, 54 mg, 58%). ir(thin film) $\bar{\nu}$ /cm⁻¹: 1720(m-s), 1660(s), 1630(s). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 166.4, 138.0, 128.8, 128.6, 126.0, 65.3, 63.9, 49.3(intense), 37.1, 24.9, 22.9, 21.8, 20.7.

1-Hydroxy-7,10-diaza-4-oxatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-12,14,16-trien-11-one (134 c)

N-[2-(Morpholin-4-yl)ethyl]phthalimide (2.0 g) was irradiated for 5 hours using the 400-watt medium-pressure lamp with a Pyrex filter. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.61 g), then (134 c) first isomer as a pale yellow oil (0.43 g, 31%). ir(thin film) $\bar{\nu}$ /cm⁻¹: 3320(broad), 1700(s), 1595(w). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 7.50 - 7.30(m, 4H); 4.92(broad, ~1H); 4.20 - 3.10(m,

6H); 2.80 - 1.85(m, 5H). ^{13}C -nmr(90 MHz, CDCl_3)
 δ /ppm: 164.8, 144.6, 131.9, 131.5, 129.8, 123.7,
 123.2, 85.4, 67.2, 66.5, 66.2, 54.4, 54.1, 35.5.
Mass Spectrum $m/e = 260(\text{M}^+)$, $242(\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2)$,
 100(base, $\text{C}_5\text{H}_{10}\text{NO}$). The second isomer was obtained
 as a pale yellow semi-solid (0.17 g, 12%). ir(CDCl_3)
 $\bar{\nu}/\text{cm}^{-1}$: 3300(broad), 1700(s), 1600(w). ^1H -nmr(90
 MHz, CDCl_3) δ /ppm: 7.75 - 7.35(m, 4H); 4.15 - 3.40(m,
 4H); 3.35 - 2.35(m, 8H). ^{13}C -nmr(90 MHz, CDCl_3)
 δ /ppm: 164.9, 143.7, 132.3, 131.5, 130.1, 123.7,
 122.5, 85.3, 62.2, 59.3(intense), 53.1, 43.1, 34.8.
Mass Spectrum $m/e = 261(\text{M}^++1, \text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_3^2\text{H})$,
 100(base, $\text{C}_5\text{H}_{10}\text{NO}$).

Attempted acid dehydration of (134 c)

Concentrated hydrochloric acid (100 mg) was added
 to the second isomer of (134 c, 100 mg) in chloroform
 (5 cm^3) and stirred at room temperature for 24
 hours. T.L.C. of the mixture showed a major spot
 corresponding to the first isomer of (134 c).

A mixture of isomers of (134 c, 200 mg) was refluxed
 in 18% aqueous hydrochloric acid (20 cm^3) for 5
 hours. T.L.C. of the mixture showed it to contain
 many products, with a major spot corresponding
 to the first isomer of (134 c), and with none of the
 second isomer remaining.

1-Hydroxy-7,11-diaza-4-oxatetracyclo[9.7.0.0^{2,7}.0^{13,18}]-octadec-13(18)-en-12-one (139)

3,4,5,6-Tetrahydro-N-[3-(morpholin-4-yl)propyl]-phthalimide (2.0 g) was irradiated for 12 hours using the 400-watt medium-pressure lamp. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (0.6 g), then (139) first isomer (0.15 g, 11%) as a brown gum. ir(CH₂Cl₂) $\bar{\nu}$ /cm⁻¹: 3310(broad), 1700(s), 1665(shoulder). ¹H-nmr (90 MHz, CDCl₃) δ /ppm: 4.05 - 3.40(m, 4H); 3.20 - 2.85(m, 2H); 2.80 - 1.20(m, 16H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.0, 153.8, 134.3, 92.5, 68.5, 66.7, 66.5, 58.8, 52.7, 39.4, 25.3, 24.3, 22.7, 21.6, 20.5. Mass Spectrum m/e = 278(M⁺), 260(C₁₅H₂₀N₂O₂), 100(base, C₅H₁₀NO). The second isomer (0.09 g, 6%) was obtained as a brown gum. ir(CH₂Cl₂) $\bar{\nu}$ /cm⁻¹: 3315 (broad), 1700(s), 1665(shoulder). ¹H-nmr(90 MHz, CDCl₃) δ /ppm: 3.90 - 2.80(m, ~ 8H); 2.35 - 1.20(m, 14H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.9, 153.8, 133.0, 90.4, 63.5, 61.1, 60.1, 54.5, 50.6, 41.3, 25.4, 22.2, 21.7, 21.2, 20.0. Mass Spectrum m/e = 278(M⁺), 260(C₁₅H₂₀N₂O₂), 100(base, C₅H₁₀NO).

2-Hydroxy-3-(morpholin-4-yl)-6-azatricyclo[6.4.0.0^{2,6}]-
dodeca-8,10,12-trien-7-one (140)

and

1-Hydroxy-7,11-diaza-4-oxatetracyclo[9.7.0.0^{2,7}.
0^{13,18}]octadeca-13,15,17-trien-12-one (141)

N-[3-(Morpholin-4-yl)propyl]phthalimide was irradiated for 16 hours using the 400-watt medium-pressure lamp with a Pyrex filter. Separation of the mixture by silica-gel column chromatography using an eluent ranging from chloroform to 10% methanol/90% chloroform gave starting material (1.10g), then (140) first product (0.09 g 10%) as a pale yellow waxy solid.

ir(CH₂Cl₂) $\bar{\nu}$ /cm⁻¹: 3260(broad), 1680(s), 1615(w).

¹H-nmr(90 MHz, CDCl₃) δ /ppm: 7.75 - 7.35(m, 4H);

3.80(t, J=4½ Hz, 4H); 3.70 - 3.25(m, 3H); 3.00

- 2.20(m, 7H). ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 170.0,

146.9, 132.5, 129.7, 123.7, 94.6, 69.2(d), 67.1

(intense, t), 52.6(intense, t), 39.4(t), 29.8(t).

Mass Spectrum ^m/_e = 274(M⁺), 188(C₁₁H₁₀NO₂), 126(base, C₇H₁₂NO). A mixture of two other products (0.16

g, 18%) was obtained which could not be further

separated by repeated column chromatography. ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 167.0, 145.4, 145.2, 132.0,

131.3, 129.8, 129.6, 124.0, 123.3, 123.2, 99.3,

91.7, 69.2, 68.8, 67.6, 67.0(intense), 66.4, 59.2,

53.3, 50.6(intense), 40.7, 40.2, 28.0, 25.4. A

second mixture of two products (0.19 g, 21%) was

also obtained which could not be further separated

by repeated column chromatography. ¹³C-nmr(90 MHz, CDCl₃) δ /ppm: 167.0, 145.8, 145.1, 132.2, 131.3,

129.8, 124.1, 123.4, 123.2, 91.7, 90.4, 68.9, 67.6, 66.4, 64.9, 62.6, 61.7, 59.3, 53.3, 52.5, 52.0, 40.4, 40.0, 25.4, 24.8. Also isolated was 3-hydroxy-2-[3-(morpholin-4-yl)propyl]isoindolin-1-one (142) as a pale brown oil (0.29 g, 32%). ir(thin film) $\bar{\nu}/\text{cm}^{-1}$: 3330(broad), 1690(s), 1620(w). ^1H -nmr(90 MHz, CDCl_3) δ/ppm : 7.85 - 7.40(m, 4H); 5.76(s, 1H); 4.70 - 4.10(m, 7H, reduced to 6H by addition of D_2O); 2.65 - 2.15(m, 8H). ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 167.5, 145.3, 132.1, 131.5, 129.3, 123.1, 122.8, 83.2, 66.0(intense), 56.6, 52.9(intense), 39.5, 23.5. Mass Spectrum $m/e = 276(\text{M}^+)$, 100(base, $\text{C}_5\text{H}_{10}\text{NO}$).

4-Benzyl-2-hydroxy-3-phenyl-4,7-diazatricyclo-
[7.4.0.0^{2,7}]trideca-9,11,13-trien-8-one (136)

Major isomer, ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 164.5, 143.7, 138.3, 135.9, 131.0, 130.7, 129.7, 128.4, 128.2, 127.3, 124.3, 123.3, 87.0, 76.6, 58.5, 52.4, 35.7. Second isomer, ^{13}C -nmr(90 MHz, CDCl_3) δ/ppm : 166.0, 143.5, 137.6, 132.7, 132.0, 131.8, 129.7, 129.5, 128.9, 128.7, 128.2, 128.1, 127.7, 123.3, 122.2, 86.9, 69.6, 58.9, 43.3, 35.6.

C H A P T E R T E N

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